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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 01	New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover!
NEWS	4	OCT 28	KOREAPAT now available on STN
NEWS	5	NOV 30	PHAR reloaded with additional data
NEWS	6	DEC 01	LISA now available on STN
NEWS	7	DEC 09	12 databases to be removed from STN on December 31, 2004
NEWS	8	DEC 15	MEDLINE update schedule for December 2004
NEWS	9	DEC 17	ELCOM reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	10	DEC 17	COMPUAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	11	DEC 17	SOLIDSTATE reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	12	DEC 17	CERAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	13	DEC 17	THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
NEWS	14	DEC 30	EPFULL: New patent full text database to be available on STN
NEWS	15	DEC 30	CAPLUS - PATENT COVERAGE EXPANDED
NEWS	16	JAN 03	No connect-hour charges in EPFULL during January and February 2005
NEWS	17	FEB 25	CA/CAPLUS - Russian Agency for Patents and Trademarks (ROSPATENT) added to list of core patent offices covered
NEWS	18	FEB 10	STN Patent Forums to be held in March 2005
NEWS	19	FEB 16	STN User Update to be held in conjunction with the 229th ACS National Meeting on March 13, 2005
NEWS	20	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADOC
NEWS	21	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	22	FEB 28	MEDLINE/LMEDLINE reloaded
NEWS	23	MAR 02	GBFULL: New full-text patent database on STN
NEWS	24	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	25	MAR 03	MEDLINE file segment of TOXCENTER reloaded

NEWS EXPRESS	JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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FILE 'HOME' ENTERED AT 17:16:38 ON 18 MAR 2005

=> fil medline biosis caplus embase wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'MEDLINE' ENTERED AT 17:17:04 ON 18 MAR 2005

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FILE 'WPIDS' ENTERED AT 17:17:04 ON 18 MAR 2005
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=> siRNA (s) (library or libraries)
L1 178 SIRNA (S) (LIBRARY OR LIBRARIES)

<------User Break------>

SEARCH ENDED BY USER

=> py>2003 and l1
L2 142 PY>2003 AND L1

=> l1 not l2
L3 36 L1 NOT L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 25 DUP REM L3 (11 DUPLICATES REMOVED)

=> t ti l4 1-25

L4 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
TI Randomized DNA libraries for generating double-stranded RNA libraries and screening nucleic acid drugs

L4 ANSWER 2 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI Preparing DNA fragment corresponding to nucleotide sequence of 5' end region of mRNA, by preparing nucleic acid corresponding to nucleotide sequence of 5' end of mRNA, cleaving nucleic acid with restriction enzyme.

L4 ANSWER 3 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI Use of a composition enriched for a protein having an activity that cleaves a dsRNA substrate for producing siRNAs that target specific genes

involved in e.g. cancer, heart disease, Alzheimer's disease, Parkinson's disease and arthritis.

L4 ANSWER 4 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI New short interfering nucleic acid downregulates expression of the c-fos gene useful for treatment and diagnosis of diseases, e.g. cancer and inflammation .

L4 ANSWER 5 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI New short interfering nucleic acid, useful e.g. for treatment and diagnosis of cancer, downregulates expression of the GRB2-associated binding protein gene.

L4 ANSWER 6 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI New short interfering nucleic acid, useful e.g. for treatment and diagnosis of cancers, downregulates expression of the multidrug resistance gene.

L4 ANSWER 7 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI Attenuating expression of a target gene in host cells comprises introducing double stranded RNA into the host cells in an amount that attenuates expression of the target gene.

L4 ANSWER 8 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI New RNAi molecule targeting a region of a polynucleotide corresponding to an exogenous sequence, useful for regulating the expression of a gene.

L4 ANSWER 9 OF 25 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Regulation of nuclear receptor transcriptional activity by a novel DEAD box RNA helicase (DP97).

L4 ANSWER 10 OF 25 MEDLINE on STN DUPLICATE 1
TI RNAi microarray analysis in cultured mammalian cells.

L4 ANSWER 11 OF 25 MEDLINE on STN DUPLICATE 2
TI Development of siRNA libraries by in vitro dicing and optimized efficient expression vectors for siRNAs in mammalian cells.

L4 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
TI RNAi-mediated gene silencing by tRNA-shRNA expression vector and diced siRNA libraries

L4 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
TI Development of siRNA expression vector and construction of siRNA expression library

L4 ANSWER 14 OF 25 MEDLINE on STN DUPLICATE 3
TI Strategies for generation of an siRNA expression library directed against the human genome.

L4 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
TI Efficient gene silencing using a diced-siRNA library

L4 ANSWER 16 OF 25 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Homeodomain interacting protein kinase 2 promotes apoptosis by downregulating the transcriptional corepressor CtBP.

L4 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
TI Preparation of siRNA library using recombinant Dicer

L4 ANSWER 18 OF 25 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN
TI RhoA is highly up-regulated in the process of early heart development of the chick and important for normal embryogenesis.

L4 ANSWER 19 OF 25 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Expressing functional siRNAs in mammalian cells using convergent transcription.

L4 ANSWER 20 OF 25 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Functional informatics for neuroscience.

L4 ANSWER 21 OF 25 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI A high throughput cell-based screen for identification of putative Alzheimer's disease modifying drugable genes that modulate amyloid levels.

L4 ANSWER 22 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI Identifying targets of effectors of gene expression or cellular activity, by contacting reporter cells with an effector, adding nucleic acid encoding a target and identifying cells with altered expression or activity.

L4 ANSWER 23 OF 25 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Physical and functional interaction between myeloid cell leukemia 1 protein (MCL1) and fortilin. The potential role of MCL1 as a fortilin chaperone.

L4 ANSWER 24 OF 25 MEDLINE on STN DUPLICATE 4
TI Mechanism of action of hammerhead ribozymes and their applications in vivo: rapid identification of functional genes in the post-genome era by novel hybrid ribozyme libraries.

L4 ANSWER 25 OF 25 MEDLINE on STN DUPLICATE 5
TI A functional gene discovery in cell differentiation by hybrid ribozyme and siRNA libraries.

=> d ibib abs l4 1-25

L4 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:3042 CAPLUS
DOCUMENT NUMBER: 140:72134
TITLE: Randomized DNA libraries for generating double-stranded RNA libraries and screening nucleic acid drugs
INVENTOR(S): Liang, Zicai; Zhang, Hong-yan; Chen, Meihong; Shen, Yan
PATENT ASSIGNEE(S): Sinogenomax Company Ltd., Peop. Rep. China
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004001044	A1	20031231	WO 2003-SE1077	20030623
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-390108P P 20020621

AB This invention relates to DNA libraries based on plasmid or viral vectors that can express double-stranded RNA of 10-30 base pairs in length with all possible sequences, where each of the double stranded RNA is formed by a single RNA mol. in the form of hairpin, or formed by two sep. RNA mols. with different 3'-overhangs. The double stranded RNAs are cell-specific, tissue-specific and organism-specific. Each single member in such a DNA library encodes all components of a double stranded RNA as specified above. Such a library can be used in screening for double stranded RNA species that can induce a given phenotype without prior knowledge of their target genes. This invention further relates to a method to generate such a DNA library, such as the one encoding all permutations of the siRNA..

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-082194 [08] WPIDS
DOC. NO. CPI: C2004-033908
TITLE: Preparing DNA fragment corresponding to nucleotide sequence of 5' end region of mRNA, by preparing nucleic acid corresponding to nucleotide sequence of 5' end of mRNA, cleaving nucleic acid with restriction enzyme.
DERWENT CLASS: B04 D16
INVENTOR(S): CARNINCI, P; HARBERS, M T; HAYASHIZAKI, Y
PATENT ASSIGNEE(S): (DNAF-N) DNAFORM KK; (RIKE) RIKEN KK
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003106672	A2	20031224	(200408)*	EN	121
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003238702	A1	20031231	(200451)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003106672	A2	WO 2003-JP7514	20030612
AU 2003238702	A1	AU 2003-238702	20030612

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003238702	A1 Based on	WO 2003106672

PRIORITY APPLN. INFO: JP 2002-235294 20020812; JP

2002-171851 20020612

AN 2004-082194 [08] WPIDS

AB WO2003106672 A UPAB: 20040202

NOVELTY - Preparing (M1) a DNA fragment (I) corresponding to a nucleotide sequence of a 5' end region of an mRNA, comprising preparing a nucleic acid (II) corresponding to a nucleotide sequence of the 5' end of an mRNA, attaching a linker to (II), cleaving (II) with a restriction enzyme having its recognition site within the linker and collecting a resulting (I) corresponding to the 5' end of the mRNA, is new.

DETAILED DESCRIPTION - Preparing (M1) a DNA fragment (I) corresponding to a nucleotide sequence of a 5' end region of an mRNA, comprises:

(a) preparing a nucleic acid (II) corresponding to a nucleotide sequence of the 5' end of an mRNA, attaching a linker to (II), cleaving (II) with a restriction enzyme having its recognition site within the linker and its cleavage site within (II) corresponding to the 5' end of the mRNA and collecting a resulting (I) corresponding to the 5' end of the mRNA; or

(b) substituting a cap structure of an mRNA with an oligonucleotide, synthesizing a first strand cDNA using the mRNA as a template, synthesizing a second strand cDNA using the first stand cDNA as a template, cleaving a resulting double stranded cDNA with the restriction enzyme and collecting a resulting (I), where the oligonucleotide comprises a restriction enzyme recognition site, and a cleavage site of a restriction enzyme in (II).

INDEPENDENT CLAIMS are also included for:

(1) a concatemer (III) prepared by (M1);

(2) a vector comprising (III); and

(3) a sequence derived from (III).

USE - (M1) is useful for the development of diagnostic tools, research tools and a reagent or a kit. (M1) is useful for preparing (I) corresponding to a nucleotide sequence of a 5' end region of an mRNA. (I) prepared by (M1) is useful for determining a nucleotide sequence of the 5' region of the mRNA which involves sequencing (I). (I) prepared by (M1) is useful for preparing a concatemer comprising one or more DNA fragments which involves ligating one or more of (I) that corresponds to the 5' end of the mRNA. (I) is useful for determining the transcriptional states of a sample, obtaining and quantifying expression data on a several of mRNAs or cDNAs in a sample, building a database holding sequence information, identifying transcribed regions from a genomic sequence and identifying a transcription initiation site and a related regulatory sequence in a genomic sequence, by a sequence derived from (I). (I) prepared by (M1) is useful for cloning a full-length or partial cDNA from a cDNA library or biological sample, cloning a complete or partial promoter region of a gene from a genomic library or genomic DNA, analyzing the activity of regulatory regions in a genome based on genomic sequence information and inactivating a gene or altering its expression, by using a sequence derived from (I), where the gene is inactivated or altered in its expression by the means of siRNA or RNA. (I) is useful for synthesizing a nucleotide sequence to be used as the linker or primer, and a hybridization on probe based on a sequence derived from (I), where the hybridization probe is attached to a support. The hybridization probe is a probe to identify the sequence corresponding to the nucleotide sequence of the 5' end region of the mRNA (all claimed).

(M1) is useful for selectively collecting multiple nucleic acid fragments containing information on the nucleotide sequences at the 5' end of multiple mRNA in a sample, analyzing complex regulatory networks in combination with the ability to identify and clone new genes opens a wide area of applications for monitoring biological systems and their status in development, homeostasis disease, and for identifying differentially expressed genes. (III) is useful for identifying regions in the genome, which are required for gene regulation and gene expression.

DESCRIPTION OF DRAWING(S) - The figure shows the flowchart explaining

the method of preparing the DNA fragment corresponding to a nucleotide sequence of a 5' end region of an mRNA.
Dwg.1/6

L4 ANSWER 3 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-877518 [81] WPIDS
DOC. NO. CPI: C2003-247943
TITLE: Use of a composition enriched for a protein having an activity that cleaves a dsRNA substrate for producing siRNAs that target specific genes involved in e.g. cancer, heart disease, Alzheimer's disease, Parkinson's disease and arthritis.
DERWENT CLASS: B04 D16
INVENTOR(S): FERRELL, J; MYERS, J
PATENT ASSIGNEE(S): (FERR-I) FERRELL J; (MYER-I) MYERS J; (STRD) UNIV LELAND STANFORD JUNIOR
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003093430	A2	20031113	(200381)*	EN	247
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2003224432	A1	20031204	(200403)		
AU 2003234336	A1	20031117	(200442)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2003093430	A2		WO 2003-US13671	20030430
US 2003224432	A1	Provisional	US 2002-377704P	20020503
		Provisional	US 2002-400655P	20020801
			US 2003-427758	20030430
AU 2003234336	A1		AU 2003-234336	20030430

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2003234336	A1	Based on	WO 2003093430

PRIORITY APPLN. INFO: US 2002-400655P 20020801; US 2002-377704P 20020503; US 2003-427758 20030430
AN 2003-877518 [81] WPIDS
AB WO2003093430 A UPAB: 20040128.
NOVELTY - Producing (M1) small interfering RNA (siRNA) from an initial double stranded RNA (dsRNA), comprising contacting the dsRNA with a composition enriched for a protein having an activity that cleaves a dsRNA substrate into fragments having siRNA activity to produce the siRNA, where the composition efficiently produces siRNAs from dsRNA.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a method (M2) of at least reducing the expression of a gene in a target cell, comprising producing an siRNA preparation for the gene using (M1), and introducing into the cell an effective amount of the siRNA preparation to at least reduce expression of the gene;

(2) a kit for use in preparing siRNA from dsRNA, comprising a composition enriched for a protein having an activity that cleaves a dsRNA substrate into fragments having siRNA activity to produce the siRNA, where the composition efficiently produces siRNAs from dsRNA; and

(3) a d-siRNA preparation produced according to (M1).

ACTIVITY - Cytostatic; Cardiant; Respiratory-Gen.; Nootropic; Neuroprotective; Antiparkinsonian; Antidiabetic; Antiarthritic. No biological data provided.

MECHANISM OF ACTION - Protein-Serine-Kinase-Inhibitor.

USE - For producing siRNA useful in reducing the expression of a gene in a target cell (claimed). Also for drug screening/target validation, large scale functional library screening, silencing single genes, and for silencing families of genes e.g. Ser/Thr kinases, phosphatases, and membrane receptors; for identifying gene function; for determining signaling pathways; and for targeting genes involved in e.g. cancer, heart disease, lung disease, Alzheimer's disease, Parkinson's disease, diabetes, and arthritis.

ADVANTAGE - Provides an inexpensive, efficient method for generating a large number of different siRNAs from a given mRNA.

Dwg.0/10

L4 ANSWER 4 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-679877 [64] WPIDS

CROSS REFERENCE: 1993-386599 [48]; 1997-259017 [23]; 1998-437449 [37]; 1999-009494 [01]; 2000-062023 [05]; 2000-062028 [05]; 2001-244406 [25]; 2002-215899 [27]; 2002-617759 [66]; 2003-140439 [13]; 2003-140484 [13]; 2003-201244 [19]; 2003-229207 [22]; 2003-671816 [63]; 2003-679850 [64]; 2003-679873 [64]; 2003-679876 [64]; 2003-679889 [64]; 2003-679891 [64]; 2003-689777 [65]; 2003-689778 [65]; 2003-689784 [65]; 2003-689785 [65]; 2003-689788 [65]; 2003-689980 [65]; 2003-689983 [65]; 2003-697557 [66]; 2003-697604 [66]; 2003-697605 [66]; 2003-697606 [66]; 2003-697608 [66]; 2003-697609 [66]; 2003-697611 [66]; 2003-697612 [66]; 2003-697624 [66]; 2003-712607 [67]; 2003-712612 [67]; 2003-712615 [67]; 2003-712622 [67]; 2003-721687 [68]; 2003-721691 [68]; 2003-731546 [69]; 2003-731605 [69]; 2003-731676 [69]; 2003-801249 [75]; 2003-901032 [82]; 2004-031273 [03]; 2004-032029 [03]; 2004-053455 [05]; 2004-071548 [07]; 2004-247781 [23]; 2004-766879 [75]; 2005-012649 [01]; 2005-040107 [04]; 2005-072857 [08]; 2005-090672 [10]; 2005-091819 [10]; 2005-112870 [12]; 2005-112874 [12]; 2005-142281 [15]; 2005-163247 [17]

DOC. NO. CPI: C2003-185787

TITLE: New short interfering nucleic acid downregulates expression of the c-fos gene useful for treatment and diagnosis of diseases, e.g. cancer and inflammation .

DERWENT CLASS: B04 D16

INVENTOR(S): BEIGELMAN, L; MCSWIGGEN, J

PATENT ASSIGNEE(S): (SIRN-N) SIRNA THERAPEUTICS INC

COUNTRY COUNT: 102

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003070914	A2	20030828	(200364)*	EN	145

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA

ZM ZW
AU 2003213163 A1 20030909 (200427)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003070914	A2	WO 2003-US5162	20030220
AU 2003213163	A1	AU 2003-213163	20030220

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003213163	A1 Based on	WO 2003070914

PRIORITY APPLN. INFO: US 2003-440129P 20030115; US
2002-358580P 20020220; US
2002-363124P 20020311; US
2002-386782P 20020606; US
2002-406784P 20020829; US
2002-408378P 20020905; US
2002-409293P 20020909

AN 2003-679877 [64] WPIDS

CR 1993-386599 [48]; 1997-259017 [23]; 1998-437449 [37]; 1999-009494 [01]; 2000-062023 [05]; 2000-062028 [05]; 2001-244406 [25]; 2002-215899 [27]; 2002-617759 [66]; 2003-140439 [13]; 2003-140484 [13]; 2003-201244 [19]; 2003-229207 [22]; 2003-671816 [63]; 2003-679850 [64]; 2003-679873 [64]; 2003-679876 [64]; 2003-679889 [64]; 2003-679891 [64]; 2003-689777 [65]; 2003-689778 [65]; 2003-689784 [65]; 2003-689785 [65]; 2003-689788 [65]; 2003-689980 [65]; 2003-689983 [65]; 2003-697557 [66]; 2003-697604 [66]; 2003-697605 [66]; 2003-697606 [66]; 2003-697608 [66]; 2003-697609 [66]; 2003-697611 [66]; 2003-697612 [66]; 2003-697624 [66]; 2003-712607 [67]; 2003-712612 [67]; 2003-712615 [67]; 2003-712622 [67]; 2003-721687 [68]; 2003-721691 [68]; 2003-731546 [69]; 2003-731605 [69]; 2003-731676 [69]; 2003-801249 [75]; 2003-901032 [82]; 2004-031273 [03]; 2004-032029 [03]; 2004-053455 [05]; 2004-071548 [07]; 2004-247781 [23]; 2004-766879 [75]; 2005-012649 [01]; 2005-040107 [04]; 2005-072857 [08]; 2005-090672 [10]; 2005-091819 [10]; 2005-112870 [12]; 2005-112874 [12]; 2005-142281 [15]; 2005-163247 [17]

AB WO2003070914 A UPAB: 20050311
NOVELTY - Short interfering nucleic acid (siNA) that down-regulates expression of the c-fos gene by RNA interference, is new.

ACTIVITY - Vasotropic; Nootropic; Antiparkinsonian; Neuroprotective; Cytostatic; Antiinflammatory; Antiallergic; Virucide; Anti-HIV; Immunosuppressive; Anticonvulsant; Nephrotropic. Test methods are described but no results are given.

MECHANISM OF ACTION - Gene Therapy; Modulation (inhibition) of expression or activity of c-fos by RNA interference (siNA target mRNA, RNA splice variants, post-transcriptionally modified RNA, pre-RNA and/or RNA templates). No biological data given.

USE - siNA are used to modulate expression of c-fos genes, in cells, tissue explants or organisms, e.g. by ex vivo gene therapy, in grafts and transplants for treating restenosis and central nervous system lesions and injuries (Alzheimer's, Parkinson's or Huntington's diseases, epilepsy, dementia or amyotrophic lateral sclerosis) or for treating many cancers, other proliferative diseases (restenosis and polycystic kidney disease), inflammatory and/or allergic diseases, viral infections (including HIV), autoimmune diseases and transplant rejection, and also for drug screening; diagnosis; target identification and validation; genetic engineering; pharmacogenomics; studying gene function and gene mapping (e.g. of single-nucleotide polymorphisms).
Dwg.0/11

L4 ANSWER 5 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-697611 [66] WPIDS
CROSS REFERENCE: 1993-386599 [48]; 1997-259017 [23]; 1998-437449 [37]; 1999-009494 [01]; 2000-062023 [05]; 2000-062028 [05]; 2001-244406 [25]; 2002-215899 [27]; 2002-617759 [66]; 2003-140439 [13]; 2003-140484 [13]; 2003-201244 [19]; 2003-229207 [22]; 2003-671816 [63]; 2003-679850 [64]; 2003-679873 [64]; 2003-679876 [64]; 2003-679877 [64]; 2003-679889 [64]; 2003-679891 [64]; 2003-689777 [65]; 2003-689778 [65]; 2003-689784 [65]; 2003-689785 [65]; 2003-689788 [65]; 2003-689980 [65]; 2003-689983 [65]; 2003-697557 [66]; 2003-697604 [66]; 2003-697605 [66]; 2003-697606 [66]; 2003-697608 [66]; 2003-697609 [66]; 2003-697612 [66]; 2003-697624 [66]; 2003-712607 [67]; 2003-712612 [67]; 2003-712615 [67]; 2003-712622 [67]; 2003-721687 [68]; 2003-721691 [68]; 2003-731546 [69]; 2003-731605 [69]; 2003-731676 [69]; 2003-801249 [75]; 2003-901032 [82]; 2004-031273 [03]; 2004-032029 [03]; 2004-053455 [05]; 2004-247781 [23]; 2004-440369 [41]; 2004-766879 [75]; 2005-012649 [01]; 2005-040107 [04]; 2005-090672 [10]; 2005-091819 [10]; 2005-112870 [12]; 2005-112874 [12]; 2005-163247 [17]
DOC. NO. CPI: C2003-191890
TITLE: New short interfering nucleic acid, useful e.g. for treatment and diagnosis of cancer, downregulates expression of the GRB2-associated binding protein gene.
DERWENT CLASS: B04 D16
INVENTOR(S): BEIGELMAN, L; MCSWIGGEN, J; USMAN, N
PATENT ASSIGNEE(S): (RIBO-N) RIBOZYME PHARM INC
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003070903	A2	20030828	(200366)*	EN	140
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003216311	A1	20030909	(200427)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003070903	A2	WO 2003-US4909	20030218
AU 2003216311	A1	AU 2003-216311	20030218

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003216311	A1 Based on	WO 2003070903

PRIORITY APPLN. INFO: US 2003-440129P 20030115; US
2002-358580P 20020220; US
2002-363124P 20020311; US
2002-386782P 20020606; US
2002-406784P 20020829; US

2002-408378P 20020905; US
2002-409293P 20020909

AN 2003-697611 [66] WPIDS

CR 1993-386599 [48]; 1997-259017 [23]; 1998-437449 [37]; 1999-009494 [01]; 2000-062023 [05]; 2000-062028 [05]; 2001-244406 [25]; 2002-215899 [27]; 2002-617759 [66]; 2003-140439 [13]; 2003-140484 [13]; 2003-201244 [19]; 2003-229207 [22]; 2003-671816 [63]; 2003-679850 [64]; 2003-679873 [64]; 2003-679876 [64]; 2003-679877 [64]; 2003-679889 [64]; 2003-679891 [64]; 2003-689777 [65]; 2003-689778 [65]; 2003-689784 [65]; 2003-689785 [65]; 2003-689788 [65]; 2003-689980 [65]; 2003-689983 [65]; 2003-697557 [66]; 2003-697604 [66]; 2003-697605 [66]; 2003-697606 [66]; 2003-697608 [66]; 2003-697609 [66]; 2003-697612 [66]; 2003-697624 [66]; 2003-712607 [67]; 2003-712612 [67]; 2003-712615 [67]; 2003-712622 [67]; 2003-721687 [68]; 2003-721691 [68]; 2003-731546 [69]; 2003-731605 [69]; 2003-731676 [69]; 2003-801249 [75]; 2003-901032 [82]; 2004-031273 [03]; 2004-032029 [03]; 2004-053455 [05]; 2004-247781 [23]; 2004-440369 [41]; 2004-766879 [75]; 2005-012649 [01]; 2005-040107 [04]; 2005-090672 [10]; 2005-091819 [10]; 2005-112870 [12]; 2005-112874 [12]; 2005-163247 [17]

AB WO2003070903 A UPAB: 20050311

NOVELTY - Short interfering nucleic acid (siNA) that downregulates expression of the GRB2-associated binding protein (GAB2) gene by RNA interference, is new.

ACTIVITY - Cytostatic; Antiinflammatory; Antiallergic.

Test methods are described but no results are given.

MECHANISM OF ACTION - Modulation (inhibition) of expression or activity of GAB2 by RNA interference. siNA target mRNA, RNA splice variants, post-transcriptionally modified RNA, pre-RNA and/or RNA templates.

USE - siNA are used to modulate expression of GAB2 genes, in cells, tissue explants or organisms, e.g. for treating cancer, inflammation and allergies, but also for drug screening; diagnosis; target identification and validation; genetic engineering; pharmacogenomics; studying gene function and gene mapping (e.g. of single-nucleotide polymorphisms).

Dwg.0/11

L4 ANSWER 6 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-697605 [66] WPIDS

CROSS REFERENCE: 1993-386599 [48]; 1997-259017 [23]; 1998-437449 [37]; 1999-009494 [01]; 2000-062023 [05]; 2000-062028 [05]; 2001-244406 [25]; 2002-215899 [27]; 2002-617759 [66]; 2003-140439 [13]; 2003-140484 [13]; 2003-201244 [19]; 2003-229207 [22]; 2003-671816 [63]; 2003-679850 [64]; 2003-679873 [64]; 2003-679876 [64]; 2003-679877 [64]; 2003-679889 [64]; 2003-679891 [64]; 2003-689777 [65]; 2003-689778 [65]; 2003-689784 [65]; 2003-689785 [65]; 2003-689788 [65]; 2003-689980 [65]; 2003-689983 [65]; 2003-697557 [66]; 2003-697604 [66]; 2003-697606 [66]; 2003-697608 [66]; 2003-697609 [66]; 2003-697611 [66]; 2003-697612 [66]; 2003-697624 [66]; 2003-712607 [67]; 2003-712612 [67]; 2003-712615 [67]; 2003-712622 [67]; 2003-721687 [68]; 2003-721691 [68]; 2003-731546 [69]; 2003-731605 [69]; 2003-731676 [69]; 2003-801249 [75]; 2003-901032 [82]; 2004-031273 [03]; 2004-032029 [03]; 2004-053455 [05]; 2004-247781 [23]; 2004-440369 [41]; 2004-766879 [75]; 2005-012649 [01]; 2005-040107 [04]; 2005-090672 [10]; 2005-091819 [10]; 2005-112870 [12]; 2005-112874 [12]; 2005-163247 [17]

DOC. NO. CPI: C2003-191884

TITLE: New short interfering nucleic acid, useful e.g. for treatment and diagnosis of cancers, downregulates expression of the multidrug resistance gene.

DERWENT CLASS: B04 D16

INVENTOR(S): BEIGELMAN, L; MCSWIGGEN, J; THOMPSON, J

PATENT ASSIGNEE(S): (RIBO-N) RIBOZYME PHARM INC
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003070884	A2	20030828	(200366)*	EN	143

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2003216255	A1	20030909	(200427)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003070884	A2	WO 2003-US4250	20030213
AU 2003216255	A1	AU 2003-216255	20030213

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2003216255	A1	Based on	WO 2003070884

PRIORITY APPLN. INFO: US 2003-440129P 20030115; US 2002-358580P 20020220; US 2002-363124P 20020311; US 2002-386782P 20020606; US 2002-406784P 20020829; US 2002-408378P 20020905; US 2002-409293P 20020909; US 2002-413714P 20020926

AN 2003-697605 [66] WPIDS

CR 1993-386599 [48]; 1997-259017 [23]; 1998-437449 [37]; 1999-009494 [01]; 2000-062023 [05]; 2000-062028 [05]; 2001-244406 [25]; 2002-215899 [27]; 2002-617759 [66]; 2003-140439 [13]; 2003-140484 [13]; 2003-201244 [19]; 2003-229207 [22]; 2003-671816 [63]; 2003-679850 [64]; 2003-679873 [64]; 2003-679876 [64]; 2003-679877 [64]; 2003-679889 [64]; 2003-679891 [64]; 2003-689777 [65]; 2003-689778 [65]; 2003-689784 [65]; 2003-689785 [65]; 2003-689788 [65]; 2003-689980 [65]; 2003-689983 [65]; 2003-697557 [66]; 2003-697604 [66]; 2003-697606 [66]; 2003-697608 [66]; 2003-697609 [66]; 2003-697611 [66]; 2003-697612 [66]; 2003-697624 [66]; 2003-712607 [67]; 2003-712612 [67]; 2003-712615 [67]; 2003-712622 [67]; 2003-721687 [68]; 2003-721691 [68]; 2003-731546 [69]; 2003-731605 [69]; 2003-731676 [69]; 2003-801249 [75]; 2003-901032 [82]; 2004-031273 [03]; 2004-032029 [03]; 2004-053455 [05]; 2004-247781 [23]; 2004-440369 [41]; 2004-766879 [75]; 2005-012649 [01]; 2005-040107 [04]; 2005-090672 [10]; 2005-091819 [10]; 2005-112870 [12]; 2005-112874 [12]; 2005-163247 [17]

AB WO2003070884 A UPAB: 20050311

NOVELTY - Short interfering nucleic acid (siNA) that downregulates expression of a multidrug resistance (MDR; P-glycoprotein) gene by RNA interference, is new.

ACTIVITY - Cytostatic.

Test methods are described but no results are given.

MECHANISM OF ACTION - Modulation (inhibition) of expression or activity of MDR by RNA interference. siNA target mRNA, RNA splice variants, post-transcriptionally modified RNA, pre-RNA and/or RNA templates.

USE - siNA are used to modulate expression of MDR genes, in cells, tissue explants or organisms, e.g. for treating multidrug-resistant cancers but also for drug screening; diagnosis; target identification and validation; genetic engineering; pharmacogenomics; studying gene function and gene mapping (e.g. of single-nucleotide polymorphisms).
Dwg.0/11

L4 ANSWER 7 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-636734 [60] WPIDS
CROSS REFERENCE: 2001-565793 [63]
DOC. NO. CPI: C2003-174123
TITLE: Attenuating expression of a target gene in host cells comprises introducing double stranded RNA into the host cells in an amount that attenuates expression of the target gene.
DERWENT CLASS: B04 D16
INVENTOR(S): BEACH, D H; BERNSTEIN, E; CAUDY, A; CONKLIN, D; HAMMOND, S; HANNON, G J; PADDISON, P J
PATENT ASSIGNEE(S): (COLD-N) COLD SPRING HARBOR LAB; (GENE-N) GENETICA INC
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003062394	A2	20030731	(200360)*	EN	150
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003210621	A1	20030902	(200422)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003062394	A2	WO 2003-US1963	20030122
AU 2003210621	A1	AU 2003-210621	20030122

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003210621	A1 Based on	WO 2003062394

PRIORITY APPLN. INFO: US 2002-55797 20020122
AN 2003-636734 [60] WPIDS
CR 2001-565793 [63]
AB WO2003062394 A UPAB: 20040331
NOVELTY - Attenuating (M1) expression of a target gene in host cells comprising introducing double stranded RNA (dsRNA) into the host cells in an amount sufficient to attenuate expression of the target gene, where the dsRNA comprises a nucleotide sequence that hybridizes under stringent conditions to an untranslated or intronic sequence of the target gene, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a composition for attenuating expression of a target gene, comprising the above dsRNA or an expression vector which, when expressed, produces the dsRNA;

(2) a pharmaceutical package comprising a pharmaceutical preparation of the dsRNA that is, or gives rise to, a short interfering dsRNA (siRNA)

in a mammalian cell and attenuates expression of a target gene, which dsRNA does not produce a significant PKR-dependent response in the mammalian cell at concentrations effective for attenuating expression of the target gene, and label or instructions (written and/or pictorial) for administering the preparation to a patient;

(3) generating siRNA;

(4) performing a business of distributing siRNA;

(5) altering the Major Histocompatibility Complex (MHC) phenotype of a donor stem cell or its progeny;

(6) a culture of donor stem cells or their progeny;

(7) performing a transplant on a patient;

(8) reducing the susceptibility of host cells to infection by a pathogen;

(9) a non-human transgenic mammal having germ line and/or somatic cells comprising a transgene encoding a dsRNA transcriptional produce that is processed to siRNA species, where transcription of the transgene attenuates expression of an endogenous target gene in at least one cell-type of the animal; and

(10) a hairpin RNA comprising a first nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence of a target gene, and a second nucleotide sequence which is a complementary inverted repeat of the first nucleotide sequence and hybridizes to the first nucleotide sequence to form a hairpin structure, which hairpin RNA attenuates expression of the target gene and does not produce a significant PKR-dependent response at concentrations effective for attenuating expression of the target gene.

USE - M1 is useful in attenuating gene expression in a cell using gene-targeted dsRNA. The stem cell is useful in manufacturing a cellular medicament for transplantation to a patient, which cellular medicament comprises stem cells or their progeny which have an altered MHC phenotype resulting from stable attenuation of expression of one or more MHC genes by introduction of dsRNA into the stem cells. The composition is used in manufacturing a medicament for attenuating expression of one or more genes in vivo (all claimed).

Dwg.0/56

L4 ANSWER 8 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-744885 [70] WPIDS

CROSS REFERENCE: 2002-583614 [62]; 2003-182496 [18]; 2004-533358 [51]

DOC. NO. CPI: C2003-204655

TITLE: New RNAi molecule targeting a region of a polynucleotide corresponding to an exogenous sequence, useful for regulating the expression of a gene.

DERWENT CLASS: B04 D16

INVENTOR(S): FINNEY, R E; LOFQUIST, A

PATENT ASSIGNEE(S): (FINN-I) FINNEY R E; (LOFQ-I) LOFQUIST A

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003143597	A1	20030731	(200370)*		40

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2003143597	A1	Provisional	US 2000-258388P	20001228
		CIP of	US 2001-28970	20011228
		Provisional	US 2002-383782P	20020530
		CIP of	US 2002-172715	20020613
			US 2002-291235	20021108

PRIORITY APPLN. INFO: US 2002-291235 20021108; US
2000-258388P 20001228; US
2001-28970 20011228; US
2002-383782P 20020530; US
2002-172715 20020613

AN 2003-744885 [70] WPIDS

CR 2002-583614 [62]; 2003-182496 [18]; 2004-533358 [51]

AB US2003143597 A UPAB: 20040810

NOVELTY - RNAi molecule targets a region of a polynucleotide corresponding to an exogenous sequence, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an expression vector comprising a polynucleotide sequence encoding an RNAi molecule;

(2) a method for reducing the expression of a gene in a cell;

(3) a method of producing a knockdown cell library;

(4) a cell comprising a polynucleotide sequence and/or a knockdown reagent that targets a sequence tag;

(5) an animal comprising the knockdown reagent;

(6) an array of knockdown cells comprising multiple groups of vessels, where each of at least two of the vessels contains a knockdown cell, where each knockdown cell comprises a knockdown reagent and is arranged in the array in a predetermined fashion;

(7) a method of regulating the expression of a gene;

(8) a method of regulating the expression of a gene;

(9) a collection of cells, where each cell comprises a different disrupted gene; and

(10) a conditional expression system.

USE - The RNAi molecule is useful for regulating the expression of a gene (claimed).

Dwg.0/2

L4 ANSWER 9 OF 25 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003269842 EMBASE

TITLE: Regulation of nuclear receptor transcriptional activity by a novel DEAD box RNA helicase (DP97).

AUTHOR: Rajendran R.R.; Nye A.C.; Frasor J.; Balsara R.D.; Martini P.G.V.; Katzenellenbogen B.S.

CORPORATE SOURCE: B.S. Katzenellenbogen, Dept. of Molec./Integrative Physiol., University of Illinois, 524 Burrill Hall, 407 S. Goodwin Ave., Urbana, IL 61801-3704, United States. katzenel@life.uiuc.edu

SOURCE: Journal of Biological Chemistry, (14 Feb 2003) 278/7 (4628-4638).
Refs: 71
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We have identified a novel DEAD box RNA helicase (97 kDa, DP97) from a breast cancer cDNA library that interacts in a hormone-dependent manner with nuclear receptors and represses their transcriptional activity. DP97 has RNA-dependent ATPase activity, and mapping studies localize the interacting regions of DP97 and nuclear receptors to the C-terminal region of DP97 and the hormone binding/activation function-2 region of estrogen receptors (ER), as well as several other nuclear receptors. Repression by DP97 maps to a small region (amino acids 589-631) that has homology to a repression domain in the corepressor protein NCoR2/SMRTe. This region of DP97 is necessary and sufficient for its

intrinsic repression activity. The N-terminal helicase region of DP97 is, however, dispensable for its transcriptional repressor activity. The knockdown of endogenous cellular DP97 by antisense DP97 or RNA interference (siRNA for DP97) results in significant enhancement of the expression of estradiol-ER-stimulated genes and attenuation of the repression of genes inhibited by the estradiol-ER. This implies that endogenous DP97 normally dampens stimulation and intensifies repression of estra-diol-ER-regulated genes. Our findings add to the growing evidence that RNA helicases can associate with nuclear receptors and function as coregulators to modulate receptor transcriptional activity.

L4 ANSWER 10 OF 25 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003463330 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14525932
TITLE: RNAi microarray analysis in cultured mammalian cells.
AUTHOR: Mousses Spyro; Caplen Natasha J; Cornelison Robert; Weaver Don; Basik Mark; Hautaniemi Sampsa; Elkahloun Abdel G; Lotufo Roberto A; Choudary Ashish; Dougherty Edward R; Suh Ed; Kallioniemi Olli
CORPORATE SOURCE: Cancer Drug Development Laboratory, Translational Genomics Research Institute (TGen), Gaithersburg, Maryland 20878, USA.. smousses@tgen.org
SOURCE: Genome research, (2003 Oct) 13 (10) 2341-7.
Journal code: 9518021. ISSN: 1088-9051.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(VALIDATION STUDIES)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031004
Last Updated on STN: 20031218
Entered Medline: 20031208

AB RNA interference (RNAi) mediated by small interfering RNAs (siRNAs) is a powerful new tool for analyzing gene knockdown phenotypes in living mammalian cells. To facilitate large-scale, high-throughput functional genomics studies using RNAi, we have developed a microarray-based technology for highly parallel analysis. Specifically, siRNAs in a transfection matrix were first arrayed on glass slides, overlaid with a monolayer of adherent cells, incubated to allow reverse transfection, and assessed for the effects of gene silencing by digital image analysis at a single cell level. Validation experiments with HeLa cells stably expressing GFP showed spatially confined, sequence-specific, time- and dose-dependent inhibition of green fluorescence for those cells growing directly on microspots containing siRNA targeting the GFP sequence. Microarray-based siRNA transfections analyzed with a custom-made quantitative image analysis system produced results that were identical to those from traditional well-based transfection, quantified by flow cytometry. Finally, to integrate experimental details, image analysis, data display, and data archiving, we developed a prototype information management system for high-throughput cell-based analyses. In summary, this RNAi microarray platform, together with ongoing efforts to develop large-scale human siRNA libraries, should facilitate genomic-scale cell-based analyses of gene function.

L4 ANSWER 11 OF 25 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003395104 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12931624
TITLE: Development of siRNA libraries by in vitro dicing and optimized efficient expression vectors for siRNAs in mammalian cells.
AUTHOR: Kawasaki Hiroaki; Miyagishi Makoto; Taira Kazunari
SOURCE: Tanpakushitsu kakusan koso. Protein, nucleic acid, enzyme,

(2003 Aug) 48 (11 Suppl) 1638-45. Ref: 46
Journal code: 0413762. ISSN: 0039-9450.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030823
Last Updated on STN: 20031028
Entered Medline: 20031027

L4 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:866904 CAPLUS
DOCUMENT NUMBER: 140:124082
TITLE: RNAi-mediated gene silencing by tRNA-shRNA expression vector and diced siRNA libraries
AUTHOR(S): Kawasaki, Hiroaki; Taira, Kazunari
CORPORATE SOURCE: Department of Chemistry and Biotechnology, School of Engineering, The University of Tokyo, Japan
SOURCE: Idenshi Igaku (2003), 7(3), 333-337
CODEN: IDIGF4; ISSN: 1343-0971
PUBLISHER: Medikaru Du
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review gives an overview of the approach for construction of siRNA library for RNAi (RNA interference) by the in vitro dicing method using recombinant Dicer RNase. Outline of the specific procedure was described with an example case of the siRNA library for the H-ras gene. The review also discussed the design of the expression vector for shRNA (short hairpin RNA) generation. Effects of the selection of promoters on cellular localization of the shRNA products and on the RNAi efficiency (in terms of mRNA cleavage processibility) were mainly discussed.

L4 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:866902 CAPLUS
DOCUMENT NUMBER: 140:124081
TITLE: Development of siRNA expression vector and construction of siRNA expression library
AUTHOR(S): Miyagishi, Makoto; Taira, Kazunari
CORPORATE SOURCE: Department of Chemistry and Biotechnology, School of Engineering, University of Tokyo, Japan
SOURCE: Idenshi Igaku (2003), 7(3), 328-332
CODEN: IDIGF4; ISSN: 1343-0971
PUBLISHER: Medikaru Du
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review. Tech. tips for constructing expression vectors that could generate siRNA for RNAi (RNA interference) efficiently were described. Design of suitable RNA conformation (hairpin conformation, etc.) for better recognition of the target RNAs, in situ stability and transportability was described. Selection of suitable promoters such as tRNA promoter and selection of vector forms (plasmid or viral) were also discussed. Strategies for construction of the RNAi library was also discussed. Topics were focused on tech. tips for screening the mRNA target site with high specificity and efficiency for gene repression.

L4 ANSWER 14 OF 25 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004111736 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15000823

TITLE: Strategies for generation of an siRNA expression library directed against the human genome.
AUTHOR: Miyagishi Makoto; Taira Kazunari
CORPORATE SOURCE: Department of Chemistry and Biotechnology, School of Engineering, University of Tokyo, Tokyo 113-8656, Japan.
SOURCE: Oligonucleotides, (2003) 13 (5) 325-33.
Journal code: 101188415. ISSN: 1545-4576.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20040306
Last Updated on STN: 20040410
Entered Medline: 20040409

AB RNA interference (RNAi) is a phenomenon whereby expression of an individual gene is specifically silenced by the introduction of a double-stranded RNA (dsRNA) whose sequence is homologous to that of the gene in question. The generation of a small interfering RNA (siRNA) expression library directed against the entire human genome is a project that requires solutions to many difficult technical problems. We present here some strategies for solving some of these problems, including the development of genetically stable and highly active siRNA expression vectors, a procedure for selection of favorable target sites, and an efficient and inexpensive procedure for constructing an siRNA expression library.

L4 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:865105 CAPLUS
DOCUMENT NUMBER: 140:105862
TITLE: Efficient gene silencing using a diced-siRNA library
AUTHOR(S): Oshima, Keisuke; Kawasaki, Hiroaki; Taira, Kazunari
CORPORATE SOURCE: Graduate School of Engineering, Department of Chemistry and Biotechnology, University of Tokyo, Tokyo, 113-0033, Japan
SOURCE: Seitai no Kagaku (2003), 54(4), 321-325
CODEN: SEKAA6; ISSN: 0370-9531
PUBLISHER: Kanehara Ichiro Kinen Igaku Iryo Shinko Zaidan
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review. The efficient methods for gene silencing in mammalian cells by gene knockout targeting with siRNAs were discussed. The gene silencing mechanism of the RNAi (RNA interference) by the siRNAs that was the basis of the strategy was described. The siRNA screening by the in vitro dicing method using Dicer RNase of dsRNA was described as an efficient approach. The use of the prepared siRNA library was presented with an example of application to H-ras gene silencing by targeting its mRNA.

L4 ANSWER 16 OF 25 EMBASE on STN
ACCESSION NUMBER: 2003438024 EMBASE
TITLE: Homeodomain interacting protein kinase 2 promotes apoptosis by downregulating the transcriptional corepressor CtBP.
AUTHOR: Zhang Q.; Yoshimatsu Y.; Hildebrand J.; Frisch S.M.; Goodman R.H.
CORPORATE SOURCE: Q. Zhang, Vollum Institute, Oregon Health and Science University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97239, United States. zhangq@ohsu.edu
SOURCE: Cell, (17 Oct 2003) 115/2 (177-186).
Refs: 31
ISSN: 0092-8674 CODEN: CELLB5
COUNTRY: United States

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Genetic knockout of the transcriptional corepressor CtBP in mouse embryo fibroblasts upregulates several genes involved in apoptosis. We predicted, therefore, that a propensity toward apoptosis might be regulated through changes in cellular CtBP. To identify pathways involved in this regulation, we screened a mouse embryo cDNA library with an E1A-CtBP complex and identified the homeodomain interacting protein kinase 2 (HIPK2), which had previously been linked to UV-directed apoptosis through its ability to phosphorylate p53. Expression of HIPK2 or exposure to UV irradiation reduced CtBP levels via a proteosome-mediated pathway. The UV effect was prevented by coexpression of kinase-inactive HIPK2 or reduction in HIPK2 levels via siRNA. Mutation of the residue phosphorylated by HIPK2 prevented UV- and HIPK2-directed CtBP clearance. Finally, reduction in CtBP levels, either by genetic knockout or siRNA, promoted apoptosis in p53-deficient cells. These findings provide a pathway for UV-induced apoptosis in cells lacking p53.

L4 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:559508 CAPLUS
DOCUMENT NUMBER: 139:210172
TITLE: Preparation of siRNA library using recombinant Dicer
AUTHOR(S): Kawasaki, Hiroaki; Taira, Kazunari
CORPORATE SOURCE: Gradaute School of Engineering, University of Tokyo, Japan
SOURCE: RNAi Jikken Purotokoru (2003), 166-171. Editor(s): Taira, Kazunari. Yodosha: Tokyo, Japan. CODEN: 69EFQK; ISBN: 4-89706-410-4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: Japanese

AB A review. Long dsRNA chains are required for efficient gene silencing by RNAi (RNA interference), however such long dsRNAs also cause non-specific repression while they have more chance to interact with specific target sequences critical for repression. To overcome this problem, the use of the libraries of the siRNAs (small interfering RNAs) that are cellular endo products of dsRNAs by the action of Dicer RNase. A detailed protocol for preparing the siRNA library by using recombinant Dicer enzyme was presented. The coverage of the procedures included sequencing of the target region used for library preparation, the target dsRNA preparation (used as Dicer enzyme substrate), in vitro processing of the dsRNA by the Dicer enzyme, PAGE separation and elution of the siRNA library.

L4 ANSWER 18 OF 25 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003177762 EMBASE
TITLE: RhoA is highly up-regulated in the process of early heart development of the chick and important for normal embryogenesis.
AUTHOR: Kaarbo M.; Crane D.I.; Murrell W.G.
CORPORATE SOURCE: W.G. Murrell, Sch. of Biomol. and Biomed. Science, Griffith University, Nathan, QLD 4111, Australia. w.murrell@mailbox.gu.edu.au
SOURCE: Developmental Dynamics, (1 May 2003) 227/1 (35-47). Refs: 50
ISSN: 1058-8388 CODEN: DEDYEI
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 001 Anatomy, Anthropology, Embryology and Histology
021 Developmental Biology and Teratology

LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have used molecular techniques, combined with classic embryological methods, to identify up-regulated genes associated with early heart development. One of the cDNAs identified and isolated by screening a chick lambda cDNA library was the small guanosine triphosphatase RhoA. RhoA has at least three different length mRNA species, each varying in the length of the 3' untranslated region. In situ hybridisation and immunocytochemistry analysis of RhoA expression show marked up-regulation in the heart-forming region. In other systems, RhoA signalling has been shown to be important for both gene expression and morphology. To investigate the function of RhoA in early heart development, we used small interfering RNAs (siRNA) in early chick embryos. Disruption of RhoA expression by siRNA treatment resulted in lack of heart tube fusion and abnormal head development. These data indicate that RhoA is important for normal embryogenesis. .COPYRGT. 2003 Wiley-Liss, Inc.

L4 ANSWER 19 OF 25 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004279008 EMBASE
TITLE: Expressing functional siRNAs in mammalian cells using convergent transcription.
AUTHOR: Tran N.; Cairns M.J.; Dawes I.W.; Arndt G.M.
CORPORATE SOURCE: G.M. Arndt, Johnson/Johnson Research Pty Ltd., 1 Central Ave., Eveleigh, NSW 1430, Australia. garndt@medau.jnj.com
SOURCE: BMC Biotechnology, (6 Nov 2003) 3/- (9p).
Refs: 34
ISSN: 1472-6750 CODEN: BBMIE6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background: The use of small interfering RNAs (siRNAs) as genetic inhibitors of gene expression has been shown to be an effective way of studying gene function in mammalian cells. Recently, different DNA vectors for expression of small hairpin RNAs (shRNAs) or co-expression of sense and antisense RNAs have been developed that direct siRNA -mediated gene silencing. One expression cassette design that has been used to express long sense and antisense RNAs in nonmammalian cell types is symmetric transcription using convergent promoters. However, convergent transcription as a way to generate functional siRNAs in mammalian cells has not been reported. This vector design permits the generation of expression constructs containing no repeat sequences, but capable of inducing RNA interference (RNAi)-mediated gene silencing. Results: With the aim of simplifying the construction of RNAi expression vectors, we report on the production and application of a novel convergent promoter cassette capable of expressing sense and antisense RNAs, that form double-stranded RNA, and mediate gene silencing in mammalian cells. We use this cassette to inhibit the expression of both the EGFP transgene and the endogenous TP53 gene. The gene silencing effect is Dicer-dependent and the level of gene inactivation achieved is comparable to that produced with synthetic siRNA. Furthermore, this expression system can be used for both short and long-term control of specific gene expression in mammalian cells. Conclusion: The experiments performed in this study demonstrate that convergent transcription can be used in mammalian cells to invoke gene-specific silencing via RNAi. This method provides an alternative to expression of shRNAs and co-expression of sense and antisense RNAs from independent cassettes or a divergent promoter. The main advantage of the present vector design is the potential to produce a functional siRNA expression cassette with no repeat sequences. Furthermore, the cassette design reported is ideal for both routine use in

controlling specific gene expression and construction of randomised RNAi expression libraries for use in unbiased forward genetic selections. .COPYRGT. 2003 Tran et al; licensee BioMed Central Ltd.

L4 ANSWER 20 OF 25 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:204387 BIOSIS
DOCUMENT NUMBER: PREV200400204930
TITLE: Functional informatics for neuroscience.
AUTHOR(S): Pinhasov, A. [Reprint Author]; Bernal, A. [Reprint Author]; Kauffman, J. [Reprint Author]; Xin, H. [Reprint Author]; Amato, F. A. [Reprint Author]; Chen, C. [Reprint Author]; Derian, C. K. [Reprint Author]; Andrade-Gordon, P. [Reprint Author]; Plata-Salaman, C. R. [Reprint Author]; Brenneman, D. E. [Reprint Author]; Ilyin, S. E. [Reprint Author]
CORPORATE SOURCE: Bioinformatics, BTA, CNS and Vascular Res. Team, Johnson and Johnson Pharmaceut. R&D, L.L.C., Spring House, PA, USA
SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 758.8. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004

AB In the present study, we established and validated: 1. An Automated High Throughput (HT) TaqMan RT-PCR-based method for quantitative mRNA expression analysis. The data demonstrate that HT-TaqMan PCR is a powerful tool that can be used for measuring low concentrations of mRNA, is highly accurate and reproducible, and is amenable to HT analysis. Results suggest that HT-TaqMan is a reliable method for the quantification of genes with low expression, investigation of neuro-immune interactions and has potential for revealing biological markers of neurodegenerative diseases. 2. An automated platform for target functional identification and validation. We utilized existing HT Screening equipment for cell-based screening and combined it with rationally designed libraries of small interfering RNA (siRNA) molecules. Once the functional screening assay is developed and validated, libraries of siRNA are tested in the system essentially in the same way as compound libraries, except that appropriate time is allowed between siRNA transfection and functional screening. In this screening process, siRNA functions as a very specific and potent inhibitor for a targeted gene. Following target identification and additional steps for validation, HT Screening against the new selected target can be conducted. In conclusion, we combined two different technologies from traditionally separate areas of drug discovery (HT Screening and Bioinformatics) and established a NEW PARADIGM-FUNCTIONAL INFORMATICS, an automated platform for target gene expression analysis and functional validation.

L4 ANSWER 21 OF 25 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:199386 BIOSIS
DOCUMENT NUMBER: PREV200400199945
TITLE: A high throughput cell-based screen for identification of putative Alzheimer's disease modifying drugable genes that modulate amyloid levels.
AUTHOR(S): Merchiers, P. [Reprint Author]; Spittaels, K. [Reprint Author]; Staes, M. [Reprint Author]; Laenen, W. [Reprint Author]; de Vos, S. [Reprint Author]; Hinnekint, S.

[Reprint Author]; Van De Poel, A. [Reprint Author]; Van Rossen, E. [Reprint Author]; Mercken, M.; Meert, T.; De Strooper, B.; Brown, R. [Reprint Author]

CORPORATE SOURCE: Galapagos Genomics NV, Mechelen, Belgium

SOURCE: Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 445.11. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004

AB Genetic linkage studies revealed segregation of mutations in APP and in APP-processing genes PS1 and PS2 with Alzheimers disease pathology and clinical phenotype. These findings underscored the disease modifying action of players involved in the amyloid cascade. The goal of our AD program is to identify novel drugable targets that modulate the levels of extracellular Abeta (Abeta). Our state of the art arrayed adenoviral platform allows automated, highly efficient induction of single genes into mammalian cells. Pre-selected libraries of adenoviruses holding cDNAs or siRNA sequences of drugable genes are applied that knock in or knock down genes, respectively. The cell-based assays we designed consist of stable hAPP HEK293 and SH-SY5Y cell lines and are configured in 384-well plate format. Two highly sensitive Abeta ELISAs are used to analyse the conditioned medium derived from infected cells: a specific Abeta1-42 ELISA and an Abetax-42 ELISA. Proof of principle for the four assays described above (HEK293 APP and SH-SY5Y APP cells subjected to Abeta1-42 and Abetax-42 ELISAs) was delivered., i.e. known modulators of APP processing such as PS1 and BACE modulate the secreted Abeta levels reproducibly, both in the knock-in and knock-down approach. Genes of different drugable classes are screened, such as GPCRs, NHR, kinases and others. Up to now, 3 new GPCRs are identified that upon overexpression modulate Abeta levels in conditioned medium in a cell specific manner. In conclusion, combining these cell-based assays with our adenoviral infection platform yield novel drugable genes that upon further validation may become potent drug targets to tackle Alzheimer's disease.

L4 ANSWER 22 OF 25 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-750492 [81] WPIDS

DOC. NO. CPI: C2002-212671

TITLE: Identifying targets of effectors of gene expression or cellular activity, by contacting reporter cells with an effector, adding nucleic acid encoding a target and identifying cells with altered expression or activity.

DERWENT CLASS: B04 D16

INVENTOR(S): AZA-BLANC, P; CALDWELL, J S; CHANDA, S K; COOKE, M P; HOGENESCH, J B; SOMIA, N V

PATENT ASSIGNEE(S): (IRMI-N) IRM LLC

COUNTRY COUNT: 100

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002072783	A2	20020919	(200281)*	EN	140

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT

RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003170642 A1 20030911 (200367)
AU 2002254212 A1 20020924 (200433)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002072783	A2	WO 2002-US7713	20020312
US 2003170642	A1 Provisional	US 2001-275266P	20010312
		US 2002-97554	20020312
AU 2002254212	A1	AU 2002-254212	20020312

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002254212	A1 Based on	WO 2002072783

PRIORITY APPLN. INFO: US 2001-275266P 20010312; US 2002-97554 20020312
AN 2002-750492 [81] WPIDS
AB WO 200272783 A UPAB: 20021216
NOVELTY - Identifying (M1) target of an effector (E) of gene expression (GE) or cellular activity (CA), comprises contacting an addressable collection (I) of reporter cells that generate an output representative of GE/CA, with (E), introducing nucleic acid (II) encoding potential target of (E) and identifying cells in (I) that exhibit expression or activity that is different in the presence of (II) than in its absence.

DETAILED DESCRIPTION - M1 Involves identifying the target of an effector or a target for an effector of GE or for CA, by providing (I), contacting the cells with an effector of GE or CA, introducing (II) (the contacting and introducing steps are performed either simultaneously or sequentially in either order), and identifying cells in (I) that exhibit expression or activity that is different in the presence of (II) than in its absence, therefore identifying the target of or for (E).

INDEPENDENT CLAIMS are also included for:

(a) identifying (M2) a function of endogenous gene by modulating the level of a product encoded by the endogenous gene, by introducing nucleic acid molecules into populations of RCs to form (I) (cells of a first cell population comprise a different introduced nucleic acid from cells of at least a second cell population), and identifying cell populations in the collection in which cells exhibit a phenotype that is different in the presence of (II) from the phenotype exhibited in its absence, therefore identifying a nucleic acid molecule that modulates the level of a product of an endogenous gene or genes that effect the phenotype and identifying the function of the endogenous gene or genes;

(b) identifying (M3) the targets of a perturbagen by modulating the level of an endogenous messenger RNA, by introducing (II) into populations of RCs to form (I), exposing the cells to a perturbagen that potentially alters a phenotype, and identifying cell populations in the collection in which cells exhibit a phenotype that is different in the presence of (II) and the perturbagen compared to the phenotype exhibited by the cells in the absence of (II) and the perturbagen;

(c) identifying a cDNA that, when expressed in a cell, causes an altered response of the cell to a biologically active molecule compared to a control cell;

(d) a database (I) produced by the above method;

(e) a combination (II) comprising (I), where RCs comprise a promoter operatively linked to a reporter gene, and a library of nucleic acid molecules; and

(f) a kit comprising (II), and optionally comprising any additional

components selected from instructions for use of the kit for identifying targets of perturbations for GE or CA, and reagents for introducing (II) into cells.

USE - M1 Is useful for identifying a target of an effector or a target for effector for gene expression or for a cellular activity (claimed).

The method is useful to perform rational target selection, by altering concentrations of components of pathways and observing the phenotypic results to permit identification of rate limiting step(s) in a pathway. The methods are useful to identify the target as characterized perturbation, such as an effector or condition.

ADVANTAGE - The method is fully automated and provides an increased throughput over conventional methods. Miniaturization and automation of transfection/transduction procedures permit comprehensive studies of phenotypes or pathways at the level of genome. The method combines the ability to measurably modulate the biological effect of a small molecule by overexpression of its target in cells, with the utility of laboratory automation and arrayed cDNA expression library formats to identify targets efficiently. As the process is automated, the speed is significantly increased and the cost is reduced.

DESCRIPTION OF DRAWING(S) - The figure shows the result of in cellulo competition experiments with HEK293:NF-kappaB reporter cells and Jurkat:NF-kappaB reporter cells.

Dwg.2/5

L4 ANSWER 23 OF 25 EMBASE on STN

ACCESSION NUMBER: 2002364129 EMBASE

TITLE: Physical and functional interaction between myeloid cell leukemia 1 protein (MCL1) and fortilin. The potential role of MCL1 as a fortilin chaperone.

AUTHOR: Zhang D.; Li F.; Weidner D.; Mnjoyan Z.H.; Fujise K.

CORPORATE SOURCE: K. Fujise, Res. Ctr. for Cardiovasc. Diseases, Inst. Molec. Med. Prev. Human Dis., 6431 Fannin St., Houston, TX 77030, United States. kenichi.fujise@uth.tmc.edu

SOURCE: Journal of Biological Chemistry, (4 Oct 2002) 277/40 (37430-37438).
Refs: 32
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Myeloid cell leukemia 1 protein (MCL1) is an anti-apoptotic protein that is structurally related to Bcl-2. Unlike other Bcl-2 family proteins that are constitutively expressed, MCL1 is inducibly expressed in cells that are recently exposed to growth and differentiation stimuli. Here, we report the identification of fortilin as a novel MCL1-interacting protein by screening of a yeast two-hybrid library with MCL1 as bait. Fortilin specifically interacted with MCL1 both in vitro and in vivo. The intracellular localization of fortilin was predominantly nuclear and identical to that of MCL1, as shown by immunostaining and confocal microscopy analysis. Fortilin, like MCL1, was rapidly inducible in serum-stimulated human aortic vascular smooth muscle cells. Although the depletion of intracellular fortilin by small interfering RNA (siRNA) against fortilin (siRNA-fortilin) did not affect intracellular MCL1 level, the depletion of intracellular MCL1 by siRNA-MCL1 was associated with the significant reduction of the fortilin protein level, without affecting the fortilin transcript numbers. In addition, a pulse-chase experiment showed that the depletion of MCL1 by siRNA-MCL1 was associated with the rapid degradation of fortilin protein, which was found quite stable in the presence of MCL1.

Furthermore, the half-life of fortilin(R21A), a point mutant of fortilin lacking the binding to MCL1, was significantly shorter than that of wild-type fortilin as shown by a pulse-chase experiment. These data suggest that MCL1, in addition to being an anti-apoptotic molecule, serves as a chaperone of fortilin, binding and stabilizing fortilin in vivo. Taken together with our previous observation that fortilin overexpression prevents cells from undergoing apoptosis (Li, F., Zhang, D., and Fujise, K. (2001) J. Biol. Chemical 276, 47542-47549), it is likely that MCL1, an anti-apoptotic protein inducible by growth and differentiation stimuli, stabilizes another anti-apoptotic protein fortilin maximizing the prosurvival environment in cells.

L4 ANSWER 24 OF 25 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2002680696 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12440992
TITLE: Mechanism of action of hammerhead ribozymes and their applications in vivo: rapid identification of functional genes in the post-genome era by novel hybrid ribozyme libraries.
AUTHOR: Takagi Y; Suyama E; Kawasaki H; Miyagishi M; Taira K
CORPORATE SOURCE: Gene Function Research Laboratory, National Institute of Advanced Industrial Science and Technology (AIST), Central 4, 1-1-1 Higashi, Tsukuba Science City 305-8562, Japan.
SOURCE: Biochemical Society transactions, (2002 Nov) 30 (Pt 6) 1145-9. Ref: 29
Journal code: 7506897. ISSN: 0300-5127.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20021121
Last Updated on STN: 20030611
Entered Medline: 20030610

AB A hammerhead ribozyme was demonstrated to be a metalloenzyme. By controlling the metal-binding ability of the hammerhead ribozyme in the presence or absence of a specific sequence of interest, we engineered an allosterically controllable ribozyme, designated the maxizyme. Hybrid ribozymes were then constructed by coupling the site-specific cleavage activity of a hammerhead ribozyme with the unwinding activity of an endogenous RNA helicase. This leads to extremely efficient cleavage of target mRNA, not only in vitro, but also in vivo, and eliminates one of the major problems arising in the application of ribozymes for cleavage of mRNA in vivo : that many target sites on the RNA were previously inaccessible to cleavage owing to secondary and/or tertiary structure formation. Since hybrid ribozymes can efficiently attack target sites within mRNA, libraries were made of hybrid ribozymes with randomized binding arms, which were then introduced into cells. This procedure made it possible to readily identify the relevant genes associated with a specific phenotype, such as in apoptosis and cancer metastasis pathways. This application of a randomized library of hybrid ribozymes represents a simple, yet powerful, method for the identification of genes associated with specific phenotypes in the post-genome era. Moreover, vector-based siRNA (short-interfering RNA for RNA interference, RNAi) can also be used for the creation of the libraries and for the subsequent confirmation of the identified genes, relevant in the examined phenotype.

L4 ANSWER 25 OF 25 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2003369514 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12903211
TITLE: A functional gene discovery in cell differentiation by

hybrid ribozyme and siRNA libraries.

AUTHOR: Kawasaki Hiroaki; Tsunemi Masaru; Iyo Mayu; Oshima Keisuke; Minoshima Hiroshi; Hamada Akira; Onuki Reiko; Suyama Eigo; Taira Kazunari

CORPORATE SOURCE: Department of Chemistry and Biotechnology, School of Engineering, University of Tokyo, 7-3-1 Hongo, Tokyo 113-8656, Japan.

SOURCE: Nucleic acids research. Supplement (2001), (2002) (2) 275-6.
Journal code: 101169367.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200309

ENTRY DATE: Entered STN: 20030808
Last Updated on STN: 20030909
Entered Medline: 20030908

AB Recently, we developed a gene discovery system that can identify functional genes using a randomized hybrid ribozyme library. In this system, inhibition of the expression of a particular gene by active ribozymes was reflected by a change in a particular phenotype, the method allowed the identification of functional genes. In the case of identification of functional genes for apoptosis pathways, we identified many pro-apoptotic genes in TNF-alpha and Fas-mediated apoptosis pathways. In this study, we tried to identify the functional genes that are necessary for the retinoic acid (RA)-induced cell differentiation using randomized ribozyme and siRNA libraries. We succeeded to identify the several differentiation factors. Therefore, our gene discovery system based on randomized ribozyme and siRNA libraries are high potential to identify the differentiation and undifferentiation factors in the post genome era.

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	123.23	123.44

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-3.65	-3.65

FILE 'STNGUIDE' ENTERED AT 17:39:16 ON 18 MAR 2005

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 11, 2005 (20050311/UP).

=> fil medline biosis caplus embase wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.14	124.58

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-3.65

FILE 'MEDLINE' ENTERED AT 17:50:34 ON 18 MAR 2005

FILE 'BIOSIS' ENTERED AT 17:50:34 ON 18 MAR 2005

FILE 'CAPLUS' ENTERED AT 17:50:34 ON 18 MAR 2005

FILE 'EMBASE' ENTERED AT 17:50:34 ON 18 MAR 2005

FILE 'WPIDS' ENTERED AT 17:50:34 ON 18 MAR 2005

=> siRNA and (family (s) (protein or gene))
L5 277 SIRNA AND (FAMILY (S) (PROTEIN OR GENE))

=> py>2003 and l5
L6 177 PY>2003 AND L5

=> l5 not l6
L7 100 L5 NOT L6

=> dup rem l7
PROCESSING IS APPROXIMATELY 1% COMPLETE FOR L7
PROCESSING COMPLETED FOR L7
L8 50 DUP REM L7 (50 DUPLICATES REMOVED)

=> t ti l8 1-50

L8 ANSWER 1 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN
TI Protein-protein interactions involved in signaling by transforming growth factor-β or TGFβ family members and uses thereof

L8 ANSWER 2 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN
TI cDNA and proteins sequences for ATRIP (ATR-interacting protein) and uses in cell cycle checkpoint signaling

L8 ANSWER 3 OF 50 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN
TI Prolonging expression of a heterologous gene in a cell infected with a vector encoding the heterologous gene, useful for treating cancer, comprises infecting the cell with a vector encoding an apoptosis inhibiting agent.

L8 ANSWER 4 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI EndoPDI, a Novel Protein-disulfide Isomerase-like Protein That Is Preferentially Expressed in Endothelial Cells Acts as a Stress Survival Factor.

L8 ANSWER 5 OF 50 MEDLINE on STN DUPLICATE 1
TI IFI16 as a negative regulator in the regulation of p53 and p21(Waf1).

L8 ANSWER 6 OF 50 MEDLINE on STN DUPLICATE 2
TI GC-GAP, a Rho family GTPase-activating protein that interacts with signaling adapters Gab1 and Gab2.

L8 ANSWER 7 OF 50 MEDLINE on STN DUPLICATE 3
TI Role of human sphingosine-1-phosphate phosphatase 1 in the regulation of intra- and extracellular sphingosine-1-phosphate levels and cell viability.

L8 ANSWER 8 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 4

TI Cdc42 is a Rho GTPase family member that can mediate insulin signaling to glucose transport in 3T3-L1 adipocytes

L8 ANSWER 9 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN
TI HdmX stimulates Hdm2-mediated ubiquitination and degradation of p53

L8 ANSWER 10 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI RNA interference reveals that endogenous Xenopus MinK-related peptides govern mammalian K(+) channel function in oocyte expression studies.

L8 ANSWER 11 OF 50 MEDLINE on STN DUPLICATE 5
TI Dynamin-like protein 1 is involved in peroxisomal fission.

L8 ANSWER 12 OF 50 MEDLINE on STN DUPLICATE 6
TI Silencing of the novel p53 target gene Snk/Plk2 leads to mitotic catastrophe in paclitaxel (taxol)-exposed cells.

L8 ANSWER 13 OF 50 MEDLINE on STN DUPLICATE 7
TI Apoptosis induction in prostate cancer cells and xenografts by combined treatment with Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand and CPT-11.

L8 ANSWER 14 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Activation of the tumour suppressor kinase LKB1 by the STE20-like pseudokinase STRAD.

L8 ANSWER 15 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI TACE cleavage of proamphiregulin regulates GPCR-induced proliferation and motility of cancer cells.

L8 ANSWER 16 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Modulation of p53 and p73 levels by cyclin G: Implication of a negative feedback regulation.

L8 ANSWER 17 OF 50 MEDLINE on STN DUPLICATE 8
TI Small RNA: can RNA interference be exploited for therapy?.

L8 ANSWER 18 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI The PAAD/PYRIN-family protein ASC/TMS1 is a dual regulator of a conserved step in NF-kappaB activation.

L8 ANSWER 19 OF 50 MEDLINE on STN DUPLICATE 9
TI siRNAs generated by recombinant human Dicer induce specific and significant but target site-independent gene silencing in human cells.

L8 ANSWER 20 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Suppression of the dual-specificity phosphatase MKP-1 enhances HIF-1 trans-activation and increases expression of EPO.

L8 ANSWER 21 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 10
TI Strategy for siRNA-based gene therapy of SARS

L8 ANSWER 22 OF 50 MEDLINE on STN DUPLICATE 11
TI ARGONAUTE4 control of locus-specific siRNA accumulation and DNA and histone methylation.

L8 ANSWER 23 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN

TI Functional genomics in Xenopus laevis: Towards transgene-driven RNA interference and cell-specific transgene expression

L8 ANSWER 24 OF 50 MEDLINE on STN DUPLICATE 12
TI Targeting E3 ubiquitin ligases for cancer therapy.

L8 ANSWER 25 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI CD13/APN transcription is induced by Ras/MapK mediated phosphorylation of Ets-2 in activated endothelial cells.

L8 ANSWER 26 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI A core function for p120-catenin in cadherin turnover.

L8 ANSWER 27 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Chemosensitivity linked to p73 function.

L8 ANSWER 28 OF 50 MEDLINE on STN DUPLICATE 13
TI Gene silencing in chick embryos with a vector-based small interfering RNA system.

L8 ANSWER 29 OF 50 MEDLINE on STN DUPLICATE 14
TI Analysis of the 3(')-hydroxyl group in Drosophila siRNA function.

L8 ANSWER 30 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Evidence that TRPC1 (transient receptor potential canonical 1) forms a Ca(2+)-permeable channel linked to the regulation of cell volume in liver cells obtained using small interfering RNA targeted against TRPC1.

L8 ANSWER 31 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Protein Phosphorylation Drug Discovery Summit - SRI conference: Targeting kinases and phosphatases for novel therapeutics: 3-5 March 2003, San Diego, CA, USA.

L8 ANSWER 32 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI In vivo analysis of the RNA interference mechanism in Trypanosoma brucei.

L8 ANSWER 33 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI The armadillo family protein p120 modulates cadherin expression by regulating cadherin internalization and degradation.

L8 ANSWER 34 OF 50 MEDLINE on STN DUPLICATE 15
TI The mammalian passenger protein TD-60 is an RCC1 family member with an essential role in prometaphase to metaphase progression.

L8 ANSWER 35 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN
TI POSH acts as a scaffold for a multiprotein complex that mediates JNK activation in apoptosis

L8 ANSWER 36 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI Biological effects on PBL of PTPN6 gene silencing by siRNA.

L8 ANSWER 37 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI RNA interference and human disease.

L8 ANSWER 38 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Differential contributions of condensin I and condensin II to mitotic chromosome architecture in vertebrate cells.

L8 ANSWER 39 OF 50 MEDLINE on STN DUPLICATE 16
TI Different isoforms of PRIP-interacting protein with methyltransferase domain/trimethylguanosine synthase localizes to the cytoplasm and nucleus.

L8 ANSWER 40 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI MYELOID CELL LEUKEMIA (MCL)-1 PROTEIN MEDIATES APOPTOSIS RESISTANCE IN CHOLANGIOCYTES.

L8 ANSWER 41 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Physical and functional interaction between myeloid cell leukemia 1 protein (MCL1) and fortilin. The potential role of MCL1 as a fortilin chaperone.

L8 ANSWER 42 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI A role of the C-terminal region of human Rad9 (hRad9) in nuclear transport of the hRad9 checkpoint complex.

L8 ANSWER 43 OF 50 MEDLINE on STN DUPLICATE 17
TI ARGONAUTE1 is required for efficient RNA interference in Drosophila embryos.

L8 ANSWER 44 OF 50 MEDLINE on STN DUPLICATE 18
TI The PAAD/PYRIN-family protein ASC is a dual regulator of a conserved step in nuclear factor kappaB activation pathways.

L8 ANSWER 45 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN
TI Endogenous and silencing-associated small RNAs in plants

L8 ANSWER 46 OF 50 MEDLINE on STN DUPLICATE 19
TI Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells.

L8 ANSWER 47 OF 50 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
TI Silencing of Bruton's tyrosine kinase (Btk) using short interfering RNA duplexes (siRNA).

L8 ANSWER 48 OF 50 MEDLINE on STN
TI Characterisation and expression of a PP1 serine/threonine protein phosphatase (PfPP1) from the malaria parasite, Plasmodium falciparum: demonstration of its essential role using RNA interference.

L8 ANSWER 49 OF 50 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
TI The PAAD/PYRIN-Family Protein ASC Is a Regulator of a Conserved Step in NF-kB Activation Pathways.

L8 ANSWER 50 OF 50 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 20
TI Biosynthesis of the linkage region of glycosaminoglycans. Cloning and activity of galactosyltransferase II, the sixth member of the β1,3-galactosyltransferase family (β3GalT6)

=> d his

(FILE 'HOME' ENTERED AT 17:16:38 ON 18 MAR 2005)

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, WPIDS' ENTERED AT 17:17:04 ON 18 MAR 2005

L1 178 SIRNA (S) (LIBRARY OR LIBRARIES)
L2 142 PY>2003 AND L1
L3 36 L1 NOT L2
L4 25 DUP REM L3 (11 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 17:39:16 ON 18 MAR 2005

FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE, WPIDS' ENTERED AT 17:50:34 ON 18 MAR 2005

L5 277 SIRNA AND (FAMILY (S) (PROTEIN OR GENE))
L6 177 PY>2003 AND L5
L7 100 L5 NOT L6
L8 50 DUP REM L7 (50 DUPLICATES REMOVED)

=> 18 not 14
L9 49 L8 NOT L4

=> d ibib abs 19 1-49

L9 ANSWER 1 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003604984 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14688465
TITLE: Targeting E3 ubiquitin ligases for cancer therapy.
AUTHOR: Sun Yi
CORPORATE SOURCE: Division of Cancer Biology, Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan 48109-0936, USA..
sunyi@umich.edu
SOURCE: Cancer biology & therapy, (2003 Nov-Dec) 2 (6) 623-9. Ref: 106
Journal code: 101137842. ISSN: 1538-4047.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20031223
Last Updated on STN: 20040914
Entered Medline: 20040913

AB E3 ubiquitin ligases are a large family of proteins that can be classified into three major structurally distinct types: N-end rule E3s, E3s containing the HECT (Homology to E6AP C-Terminus) domain, and E3s with the RING (Really Interesting New Gene) finger, including its derivatives, the U- Box and the PHD (Plant Homeo-Domain). E3 ubiquitin ligases exist as single polypeptide or multimeric complexes. Together with ubiquitin activating enzyme E1 and ubiquitin conjugating enzyme E2, E3 ubiquitin ligases catalyze the ubiquitination of a variety of protein substrates for targeted degradation via the 26S proteasome. E3 ubiqutin ligases, therefore, play an essential role in regulation of many biological processes. Furthermore, E3s are enzymes that determine the specificity of protein substrates; they represent a class of "drugable" targets for pharmaceutical intervention. In this review, I will mainly focus on E3 ubiquitin ligases as potential cancer targets and discuss three of the most promising E3s, Mdm2/Hdm2, IAPs, and SCF, for their target rationales, target validation, and critical issues associated with them. These E3 ligases or their components are overexpressed in many

human cancers and their inhibition leads to growth suppression or apoptosis. In addition, I will evaluate two current methodologies available for the high throughput screening for small molecular weight chemical inhibitors of the E3 ubiquitin ligases. Although targeting E3 ubiquitin ligases is still in its infancy, speedy approval of the general proteasome inhibitor, Velcade (bortezomib) by the FDA for the treatment of relapsed and refractory multiple myeloma suggests the promise of specific E3 inhibitors in anti-cancer therapy. Emerging technologies, such as siRNA, will provide a better validation of many E3s. It is anticipated that E3 ubiquitin ligases will represent an important new target platform for future mechanism-driven drug discovery.

L9 ANSWER 2 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003509735 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14585643
TITLE: Small RNA: can RNA interference be exploited for therapy?.
AUTHOR: Wall Nathan R; Shi Yang
CORPORATE SOURCE: Department of Pathology, Harvard Medical School, Boston, MA 02115, USA.
CONTRACT NUMBER: F32 CA097802 (NCI)
R01GM53874 (NIGMS)
SOURCE: Lancet, (2003 Oct 25) 362 (9393) 1401-3. Ref: 39
Journal code: 2985213R. ISSN: 1474-547X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031031
Last Updated on STN: 20040113
Entered Medline: 20040112

AB CONTEXT: RNA interference (RNAi) is the sequence-specific gene-silencing induced by double-stranded RNA (dsRNA), and gives information about gene function quickly, easily, and inexpensively. The use of RNAi for genetic-based therapies is widely studied, especially in viral infections, cancers, and inherited genetic disorders. RNAi has been used to make tissue-specific knockdown mice for studying gene function in a whole animal. Combined with genomics data, RNAi-directed gene-silencing could allow functional determination of any gene expressed in a cell or pathway. The term RNAi came from the discovery that the injection of dsRNAs into Caenorhabditis elegans interferes with the expression of specific genes containing a complementary region to the delivered dsRNA. Although stalled for a time by the non-gene-specific interferon response elicited by dsRNA molecules longer than about 30 nucleotides in mammalian cells, Tom Tuschl's group found that transfection of synthetic 21-nucleotide small-interfering RNA (siRNA) duplexes were highly selective and sequence-specific inhibitors of endogenous genes. STARTING POINT: siRNA expression has been studied with siRNA from plasmid and viral vectors that efficiently deliver siRNAs into both dividing and non-dividing cells, stem cells, zygotes, and their differentiated progeny. A collection of RNA interference vectors that suppress 50 human de-ubiquitinating enzymes allowed Thijn Brummelkamp and colleagues to study this gene family and to identify de-ubiquitinating enzymes in cancer-relevant pathways (Nature 2003; 424: 797-801). These researchers found that the familial cylindromatosis tumour suppressor gene (CYLD), previously of unknown function, could enhance the activation of the transcription factor NF-kappaB, leading to increased resistance to apoptosis. They have now started to investigate the use of CYLD inhibitors in clinical trials. WHERE NEXT: The ability to efficiently and stably produce and deliver sufficient amounts of siRNA to the proper target tissues require refinement before this

new technology can be tried clinically. Initial in-vivo studies reported effective transgene suppression in adult mice by chemically synthesised siRNAs. More recently many researchers have used plasmid and viral vectors for transcription of short-hairpin RNAs, both in vitro and in vivo. With these expression systems, gene expression was more stably inhibited than with the transient knockdown recorded with chemically synthesised siRNA. Human trials exploiting these latest findings are likely to soon follow.

L9 ANSWER 3 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003507115 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12057017
TITLE: Characterisation and expression of a PP1 serine/threonine protein phosphatase (PfPP1) from the malaria parasite, Plasmodium falciparum: demonstration of its essential role using RNA interference.
AUTHOR: Kumar Rajinder; Adams Brian; Oldenburg Anja; Musiyenko Alla; Barik Sailen
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology (MSB 2370), University of South Alabama, College of Medicine, 307 University Blvd, Mobile, AL 36688-0002, USA.. rkumar@usamail.usouthal.edu
CONTRACT NUMBER: AI45803 (NIAID)
SOURCE: Malaria journal [electronic resource], (2002 Apr 26) 1 (1) 5. Electronic Publication: 2002-04-26.
Journal code: 101139802. ISSN: 1475-2875.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20031030
Last Updated on STN: 20040117
Entered Medline: 20040116

AB BACKGROUND: Reversible protein phosphorylation is relatively unexplored in the intracellular protozoa of the Apicomplexa family that includes the genus Plasmodium, to which belong the causative agents of malaria. Members of the PP1 family represent the most highly conserved protein phosphatase sequences in phylogeny and play essential regulatory roles in various cellular pathways. Previous evidence suggested a PP1-like activity in Plasmodium falciparum, not yet identified at the molecular level. RESULTS: We have identified a PP1 catalytic subunit from P. falciparum and named it PfPP1. The predicted primary structure of the 304-amino acid long protein was highly similar to PP1 sequences of other species, and showed conservation of all the signature motifs. The purified recombinant protein exhibited potent phosphatase activity in vitro. Its sensitivity to specific phosphatase inhibitors was characteristic of the PP1 class. The authenticity of the PfPP1 cDNA was further confirmed by mutational analysis of strategic amino acid residues important in catalysis. The protein was expressed in all erythrocytic stages of the parasite. Abrogation of PP1 expression by synthetic short interfering RNA (siRNA) led to inhibition of parasite DNA synthesis. CONCLUSIONS: The high sequence similarity of PfPP1 with other PP1 members suggests conservation of function. Phenotypic gene knockdown studies using siRNA confirmed its essential role in the parasite. Detailed studies of PfPP1 and its regulation may unravel the role of reversible protein phosphorylation in the signalling pathways of the parasite, including glucose metabolism and parasitic cell division. The use of siRNA could be an important tool in the functional analysis of Apicomplexan genes.

L9 ANSWER 4 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003477676 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12925527
TITLE: IFI16 as a negative regulator in the regulation of p53 and p21(Waf1).
AUTHOR: Kwak Jennifer C; Ongusaha Pat P; Ouchi Toru; Lee Sam W
CORPORATE SOURCE: Hematology and Oncology Division, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02115, USA.
CONTRACT NUMBER: CA78356 (NCI)
CA85214 (NCI)
CA85681 (NCI)
SOURCE: Journal of biological chemistry, (2003 Oct 17) 278 (42) 40899-904. Electronic Publication: 2003-08-18.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031015
Last Updated on STN: 20031219
Entered Medline: 20031203

AB IFI16 is a member of the HIN-200 family (hematopoietic interferon-inducible nuclear antigens with 200 amino acid repeats) that contains a DNA binding domain, a transcriptional regulatory domain, and DAPIN/PAAD, a protein domain associated with interferon response. It can function as a transcription repressor and directly binds p53. Although the structural and biochemical properties of IFI16 are known, the physiological relevance of these properties in the cellular context is still elusive. Here we report that the inhibition of endogenous IFI16 expression by small interfering RNA (siRNA) induces p21Waf1 mRNA and protein expression through p53 but does not induce pro-apoptotic p53 target genes. This rapid induction of p21 was wild-type p53-dependent and resulted in cell cycle arrest along with a marked reduction of phosphorylated Rb in normally growing cells. We also showed that the repression of IFI16 affects p53 transcriptional activity at the p21 promoter as well as the protein stability of p53 and p21. Our findings identified a new role for IFI16 in modulating p53 function and its target gene regulation in the control of cell cycle regulation.

L9 ANSWER 5 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003432868 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12943661
TITLE: Different isoforms of PRIP-interacting protein with methyltransferase domain/trimethylguanosine synthase localizes to the cytoplasm and nucleus.
AUTHOR: Enunlu Izzet; Papai Gabor; Cserpan Imre; Udvardy Andor; Jeang Kuan-Teh; Boros Imre
CORPORATE SOURCE: Institute of Biochemistry, Szeged, Hungary.
SOURCE: Biochemical and biophysical research communications, (2003 Sep 12) 309 (1) 44-51.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030917
Last Updated on STN: 20031017
Entered Medline: 20031016

AB A protein family including the recently identified PIMT/Tgs1 (PRIP-interacting protein with methyltransferase domain/trimethylguanosine synthase) was identified by searching databases for homologues of a newly identified Drosophila protein with

RNA-binding activity and methyltransferase domain. Antibodies raised against a short peptide of the mammalian homologue show a 90-kDa isoform expressed specifically in rat brain and testis and a 55-kDa form expressed ubiquitously. In HeLa cells, the larger isoform of the protein is nuclear and associated with a 600-kDa complex, while the smaller isoform is mainly cytoplasmic and co-localizes to the tubulin network. Inhibition of PIMT/Tgs1 expression by siRNA in HeLa cells resulted in an increase in the percentage of cells in G2/M phases. In yeast two-hybrid and in vitro GST pull down experiments, the conserved C-terminal region of PIMT/Tgs1 interacted with the WD domain containing EED/WAIT-1 that acts as a polycomb-type repressor in the nucleus and also binds to integrins in the cytoplasm. Our experiments, together with earlier data, indicate that isoforms of the PIMT/Tgs1 protein with an RNA methyltransferase domain function both in the nucleus and in the cytoplasm and associate with both elements of the cytoskeletal network and nuclear factors known to be involved in gene regulation.

L9 ANSWER 6 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003426178 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12815058
TITLE: Role of human sphingosine-1-phosphate phosphatase 1 in the regulation of intra- and extracellular sphingosine-1-phosphate levels and cell viability.
AUTHOR: Johnson Korey R; Johnson Kristy Y; Becker Kevin P; Bielawski Jacek; Mao Cungui; Obeid Lina M
CORPORATE SOURCE: Department of Medicine, Medical University of South Carolina, Charleston, South Carolina 29425, USA.
CONTRACT NUMBER: 1P20RR17677 (NCRR)
GM62287 (NIGMS)
HL 07260 (NHLBI)
SOURCE: Journal of biological chemistry, (2003 Sep 5) 278 (36) 34541-7. Electronic Publication: 2003-06-18.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030912
Last Updated on STN: 20031008
Entered Medline: 20031007

AB Sphingosine-1-phosphate (S1P) is a highly bioactive lipid that exerts numerous biological effects both intracellularly as a second messenger and extracellularly by binding to its G-protein-coupled receptors of the endothelial differentiation gene family (S1P receptors-(1-5)). Intracellularly, at least two enzymes, sphingosine kinase and S1P phosphatase, regulate the activity of S1P by governing the phosphorylation status of S1P. To study the regulation of S1P levels, we cloned the human isoform of S1P phosphatase 1 (hSPPase1). The hSPPase1 has 78% homology to the mouse SPPase at the amino acid level with 6-8 possible transmembrane domains. Confocal microscopy revealed green fluorescent protein-tagged hSPPase1, expressed in either MCF7 or HEK293 cells, co-localized to endoplasmic reticulum with calreticulin. According to Northern blot analysis, hSPPase1 is expressed in most tissues, with the strongest levels found in the highly vascular tissues of placenta and kidney. Transient overexpression of hSPPase1 exhibited a 2-fold increase in phosphatase activity against S1P and dihydro-S1P, indicating that the expressed protein was functional. Small interfering RNA (siRNA) knockdown of endogenous hSPPase1 drastically reduced hSPPase1 mRNA levels, as confirmed by reverse transcription PCR, and resulted in an overall 25% reduction of in vitro phosphatase activity in the membrane fractions. Sphingolipid mass measurements in hSPPase1 siRNA knockdown cells revealed a 2-fold increase of S1P levels and concomitant decrease in

sphingosine. In vivo labeling of hSPPase1 siRNA-treated cells showed accumulation of S1P within cells, as well as significantly increased secretion of S1P into the media, indicating that hSPPase1 regulates secreted S1P. In addition, siRNA-induced knockdown of hSPPase1 endowed resistance to tumor necrosis factor-alpha and the chemotherapeutic agent daunorubicin. Collectively, these data suggest that regulation of hSPPase1 with the resultant changes in cellular and secreted S1P could have important implications to cell proliferation, angiogenesis, and apoptosis.

L9 ANSWER 7 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003411512 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12950277
TITLE: Gene silencing in chick embryos with a vector-based small interfering RNA system.
AUTHOR: Katahira Tatsuya; Nakamura Harukazu
CORPORATE SOURCE: Laboratory of Molecular Neurobiology, Institute of Development, Aging and Cancer (IDAC), Tohoku University, Seiryo-machi 4-1, Aoba-ku, Sendai 980-8575, Japan.
SOURCE: Development, growth & differentiation, (2003 Aug) 45 (4) 361-7.
Journal code: 0356504. ISSN: 0012-1592.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 20030903
Last Updated on STN: 20040528
Entered Medline: 20040527

AB In this paper, the use of vector-based RNA interference (RNAi) to specifically interfere with gene expression in chick embryos is reported. In ovo electroporation was carried out to transfer a small interfering RNA (siRNA) expression vector into chick embryos. En2 was chosen for the target gene because the family gene, En1, is expressed in a similar pattern. Four sets of 19-mer sequences were designed with the En2 open reading frame region connected to a sequence of short hairpin RNA (shRNA), which exerts siRNA effects after being transcribed, and inserted into pSilencer U6-1.0 vector. En2 and En1 expression were suppressed by the siRNA whose sequence completely matched En2 and En1. Suppression occurred when the siRNA sequence differed by up to two nucleotides from the target sequence. The sequence that differed by four nucleotides from the target gene did not show siRNA effects. One set that completely matched the En2 target did not show siRNA effects, which may be due to location of the siRNA in the target gene. Thus, multiple sets of shRNA must be prepared if we are to consider. This system will greatly contribute to the analysis of function of genes of interest, because the target gene can be silenced in a locally and temporally desired manner.

L9 ANSWER 8 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003410281 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12819203
TITLE: GC-GAP, a Rho family GTPase-activating protein that interacts with signaling adapters Gab1 and Gab2.
AUTHOR: Zhao Chunmei; Ma Hong; Bossy-Wetzel Ella; Lipton Stuart A; Zhang Zhuohua; Feng Gen-Sheng
CORPORATE SOURCE: Burnham Institute, La Jolla, California 92037, USA.
CONTRACT NUMBER: R01GM53660 (NIGMS)
R01HL66208 (NHLBI)
SOURCE: Journal of biological chemistry, (2003 Sep 5) 278 (36)

34641-53. Electronic Publication: 2003-06-19.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030903
Last Updated on STN: 20031008
Entered Medline: 20031007

AB Gab1 and Gab2 are scaffolding proteins acting downstream of cell surface receptors and interact with a variety of cytoplasmic signaling proteins such as Grb2, Shp-2, phosphatidylinositol 3-kinase, Shc, and Crk. To identify new binding partners for GAB proteins and better understand their functions, we performed a yeast two-hybrid screening with hGab2-(120-587) as bait. This work led to identification of a novel GTPase-activating protein (GAP) for Rho family GTPases. The GAP domain shows high similarity to the recently cloned CdGAP and displays activity toward RhoA, Rac1, and Cdc42 in vitro. The protein was named GC-GAP for its ability to interact with GAB proteins and its activity toward Rac and Cdc42. GC-GAP is predominantly expressed in the brain with low levels detected in other tissues. Antibodies directed against GC-GAP recognized a protein of approximately 200 kDa. Expression of GC-GAP in 293T cells led to a reduction in active Rac1 and Cdc42 levels but not RhoA. Suppression of GC-GAP expression by siRNA inhibited proliferation of C6 astroglioma cells. In addition, GC-GAP contains several classic proline-rich motifs, and it interacts with the first SH3 domain of Crk and full-length Nck in vitro. We propose that Gab1 and Gab2 in cooperation with other adapter molecules might regulate the cellular localization of GC-GAP under specific stimuli, acting to regulate precisely Rac and Cdc42 activities. Given that GC-GAP is specifically expressed in the nervous system and that it is localized to the dendritic processes of cultured neurons, GC-GAP may play a role in dendritic morphogenesis and also possibly in neural/glial cell proliferation.

L9 ANSWER 9 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003383458 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12919680
TITLE: The mammalian passenger protein TD-60 is an RCC1 family member with an essential role in prometaphase to metaphase progression.
COMMENT: Comment in: Dev Cell. 2003 Aug;5(2):187-8. PubMed ID: 12919667
AUTHOR: Mollinari Cristiana; Reynaud Caroline; Martineau-Thuillier Stephanie; Monier Solange; Kieffer Sylvie; Garin Jerome; Andreassen Paul R; Boulet Annick; Goud Bruno; Kleman Jean-Philippe; Margolis Robert L
CORPORATE SOURCE: Institut de Biologie Structurale J-P Ebel, CEA-CNRS, 41 rue Jules Horowitz, 38027 Cedex 1, Grenoble, France.
SOURCE: Developmental cell, (2003 Aug) 5 (2) 295-307.
Journal code: 101120028. ISSN: 1534-5807.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AJ421269
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20030816
Last Updated on STN: 20031004
Entered Medline: 20031003

AB Passenger proteins migrate from inner centromeres to the spindle midzone during late mitosis, and those described to date are essential both for proper chromosome segregation and for completion of cell cleavage. We

have purified and cloned the human passenger protein TD-60, and we here report that it is a member of the RCC1 family and that it binds preferentially the nucleotide-free form of the small G protein Rac1. Using siRNA, we further demonstrate that the absence of TD-60 substantially suppresses overall spindle assembly, blocks cells in prometaphase, and activates the spindle assembly checkpoint. These defects suggest TD-60 may have a role in global spindle assembly or may be specifically required to integrate kinetochores into the mitotic spindle. The latter is consistent with a TD-60 requirement for recruitment of the passenger proteins survivin and Aurora B, and suggests that like other passenger proteins, TD-60 is involved in regulation of cell cleavage.

L9 ANSWER 10 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003372276 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12907654
TITLE: Apoptosis induction in prostate cancer cells and xenografts by combined treatment with Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand and CPT-11.
AUTHOR: Ray Subrata; Almasan Alex
CORPORATE SOURCE: Department of Cancer Biology, NB40 Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH 44195, USA.
CONTRACT NUMBER: CA 81504 (NCI)
CA 82858 (NCI)
SOURCE: Cancer research, (2003 Aug 1) 63 (15) 4713-23.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030809
Last Updated on STN: 20030924
Entered Medline: 20030923

AB Because apoptosis is deregulated in most cancers, apoptosis-modulating approaches offer an attractive opportunity for clinical therapy of many tumors, including that of the prostate. LNCaP-derived C4-2 human prostate cancer cells are quite resistant to treatment with Apo2 ligand (Apo2L) or tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), when using a nontagged, Zn-bound recombinant trimeric version that is devoid of any exogeneous sequences and therefore least likely to be immunogenic in human patients and that has been optimized for maximum efficacy and minimum toxicity. When combined with the topoisomerase I inhibitor CPT-11 (irinotecan), Apo2L/TRAIL exhibits enhanced apoptotic activity in C4-2 cells cultured in vitro as well as xenografted as tumors in vivo. Apoptosis both in vitro and in vivo was characterized by two major molecular events. First, apoptosis induction was accompanied by changes in expression levels of the Bcl-2 family genes and their products. However, whereas combination treatment applied to in vitro cell culture was characterized by a significant up-regulation and activation of Bax and down-regulation of Bcl-xL, the treatment applied to tumors induced Bak and Bcl-xS, whereas Bcl-omega and Bcl-xL were down-regulated. Because there are multiple members of the Bcl-2 family (24 members to date), these data indicate that, under different biological conditions, different proteins may be responsible for activating apoptosis and provide evidence for a differential regulation of the multidomain Bcl-2 protein -encoding genes, bax and bak. Increased Bax expression led to its activation, translocation to the mitochondria, and release of cytochrome c. In addition, this combination treatment induced apoptosis through potent activation of caspase-8 and the proapoptotic protein Bid, resulting in activation of effector caspase-3 and cleavage of its cellular target protein, poly(ADP-ribose) polymerase (PARP), events blocked by the

pan-caspase inhibitor N-tert-butoxy-carbonyl-Val-Ala-Asp-fluoro methylketone (zVAD-fmk). Activation of multiple caspases and PARP cleavage were also observed in the C4-2 tumors treated with doses resulting in effective tumor control at 42 days after Apo2L/TRAIL plus CPT-11 treatment. Down-regulation of Bax by small interference (RNA) (siRNA) in C4-2 cells significantly prevented PARP cleavage and apoptosis. Strikingly, similar experiments in cells stably expressing a dominant-negative death receptor DR5 led to complete ablation of PARP cleavage and apoptosis, indicating the essential role of both mitochondrial and receptor-mediated apoptotic pathways. Our data indicate that the combined treatment of Apo2L/TRAIL and CPT-11 achieves tumor control in prostate cancer tumors through regulation of Bcl-2 family proteins and potent activation of caspases.

L9 ANSWER 11 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003363907 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12897130
TITLE: Silencing of the novel p53 target gene Snk/Plk2 leads to mitotic catastrophe in paclitaxel (taxol)-exposed cells.
AUTHOR: Burns Timothy F; Fei Peiwen; Scata Kimberly A; Dicker David T; El-Deiry Wafik S
CORPORATE SOURCE: Laboratory of Molecular Oncology and Cell Cycle Regulation, Howard Hughes Medical Institute, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104, USA.
CONTRACT NUMBER: PO1 CA75138 (NCI)
T32 CA09677 (NCI)
SOURCE: Molecular and cellular biology, (2003 Aug) 23 (16) 5556-71. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030805
Last Updated on STN: 20030830
Entered Medline: 20030829

AB Loss of p53 sensitizes to antimicrotubule agents in human tumor cells, but little is known about its role during mitosis. We have identified the Polo-like kinase family member serum inducible kinase (Snk/Plk2) as a novel p53 target gene. Snk/Plk2 mutagenesis demonstrated that its kinase activity is negatively regulated by its C terminus. Small interfering RNA (siRNA)-mediated Snk/Plk2 silencing in the presence of the mitotic poisons paclitaxel (Taxol) or nocodazole significantly increased apoptosis, similar to p53 mutations, which confer paclitaxel sensitivity. Furthermore, we have demonstrated that the apoptosis due to silencing of Snk/Plk2 in the face of spindle damage occurs in mitotic cells and not in cells that have progressed to a G(1)-like state without dividing. Since siRNA directed against Snk/Plk2 promoted death of paclitaxel-treated cells in mitosis, we envision a mitotic checkpoint wherein p53-dependent activation of Snk/Plk2 prevents mitotic catastrophe following spindle damage. Finally, these studies suggest that disruption of Snk/Plk2 may be of therapeutic value in sensitizing paclitaxel-resistant tumors.

L9 ANSWER 12 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003301988 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12828948
TITLE: Analysis of the 3(')-hydroxyl group in Drosophila siRNA function.
AUTHOR: Wei Qin; Lipardi Concetta; Paterson Bruce M
CORPORATE SOURCE: Laboratory of Biochemistry, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.

SOURCE: Methods (San Diego, Calif.), (2003 Aug) 30 (4) 337-47.
Journal code: 9426302. ISSN: 1046-2023.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20030628
Last Updated on STN: 20040221
Entered Medline: 20040220

AB Members of the RNA-dependent RNA polymerase (RdRP) gene family have been shown to be essential for dsRNA-mediated gene silencing based on genetic screens in a variety of organisms, including Caenorhabditis elegans, Arabidopsis, Neurospora, and Dictyostelium. A hallmark of this process is the formation of small 21- to 25-bp dsRNAs, termed siRNAs for small interfering RNAs, which are derived from the dsRNA that initiates gene silencing. We have developed methods to demonstrate that these siRNAs produced in Drosophila embryo extract can be uniformly incorporated into dsRNA in a template-specific manner that is subsequently degraded by RNase III-related enzyme activity to create a second generation of siRNAs. SiRNA function in dsRNA synthesis and mRNA degradation depends upon the integrity of the 3'-hydroxyl of the siRNA, consistent with the interpretation that siRNAs serve as primers for RdRP activity in the formation of dsRNA. This process of siRNA incorporation into dsRNA followed by degradation and the formation of new siRNAs has been termed "degradative PCR" and the proposed mechanism is consistent with the genetic and biochemical data derived from studies in C. elegans, Arabidopsis, Drosophila, and Dictyostelium. The methods used to study the function of both natural and synthetic siRNAs in RNA interference in Drosophila embryo extracts are detailed. The importance of the 3'-hydroxyl group for siRNA function and its incorporation into dsRNA is emphasized and the results support a model that places RNA-dependent RNA polymerase as a key mediator in the RNA interference mechanism in Drosophila.

L9 ANSWER 13 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003114315 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12499366
TITLE: Dynamin-like protein 1 is involved in peroxisomal fission.
AUTHOR: Koch Annett; Thiemann Meinolf; Grabenbauer Markus; Yoon Yisang; McNiven Mark A; Schrader Michael
CORPORATE SOURCE: Department of Cell Biology and Cell Pathology, University of Marburg, Robert Koch Str. 5, Germany.
SOURCE: Journal of biological chemistry, (2003 Mar 7) 278 (10) 8597-605. Electronic Publication: 2002-12-23.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030312
Last Updated on STN: 20030424
Entered Medline: 20030423

AB The mammalian dynamin-like protein 1 (DLP1), a member of the dynamin family of large GTPases, possesses mechanochemical properties known to constrict and tubulate membranes. In this study, we have combined two experimental approaches, induction of peroxisome proliferation by Pex11pbeta and expression of dominant-negative mutants, to test whether DLP1 plays a role in peroxisomal growth and division. We were able to localize DLP1 in spots on tubular peroxisomes in HepG2 cells. In addition, immunoblot analysis revealed the presence of DLP1 in highly purified peroxisomal fractions from rat liver and an increase of DLP1

after treatment of rats with the peroxisome proliferator bezafibrate. Expression of a dominant negative DLP1 mutant deficient in GTP hydrolysis (K38A) either alone or in combination with Pex11pbeta caused the appearance of tubular peroxisomes but had no influence on their intracellular distribution. In co-expressing cells, the formation of tubulo-reticular networks of peroxisomes was promoted, and peroxisomal division was completely inhibited. These findings were confirmed by silencing of DLP1 using siRNA. We propose a direct role for the dynamin-like protein DLP1 in peroxisomal fission and in the maintenance of peroxisomal morphology in mammalian cells.

L9 ANSWER 14 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003051836 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12560494
TITLE: siRNAs generated by recombinant human Dicer induce specific and significant but target site-independent gene silencing in human cells.
AUTHOR: Kawasaki Hiroaki; Suyama Eigo; Iyo Mayu; Taira Kazunari
CORPORATE SOURCE: Department of Chemistry and Biotechnology, School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656, Japan.
SOURCE: Nucleic acids research, (2003 Feb 1) 31 (3) 981-7. Journal code: 0411011. ISSN: 1362-4962.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030204
Last Updated on STN: 20030307
Entered Medline: 20030306

AB RNA interference has emerged as a powerful tool for the silencing of gene expression in animals and plants. It was reported recently that 21 nt synthetic small interfering RNAs (siRNAs) specifically suppressed the expression of endogenous genes in several lines of mammalian cells. However, the efficacy of siRNAs is dependent on the presence of a specific target site within the target mRNA and it remains very difficult to predict the best or most effective target site. In this study, we demonstrate that siRNAs that have been generated in vitro by recombinant human Dicer (re-hDicer) significantly suppress not only the exogenous expression of a puromycin-resistance gene but also the endogenous expression of H-ras, c-jun and c-fos. In our system, selection of a target site is not necessary in the design of siRNAs. However, it is important to avoid homologous sequences within a target mRNA in a given protein family. Our diced siRNA system should
be a powerful tool for the inactivation of genes in mammalian cells.

L9 ANSWER 15 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003050982 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12522258
TITLE: ARGONAUTE4 control of locus-specific siRNA accumulation and DNA and histone methylation.
AUTHOR: Zilberman Daniel; Cao Xiaofeng; Jacobsen Steven E
CORPORATE SOURCE: Department of Molecular, Cell, and Developmental Biology, Molecular Biology Institute, University of California, Los Angeles, CA 90095-1606.
CONTRACT NUMBER: GM07185 (NIGMS)
GM60398 (NIGMS)
SOURCE: Science, (2003 Jan 31) 299 (5607) 716-9. Electronic Publication: 2003-01-09. Journal code: 0404511. ISSN: 1095-9203.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030202
Last Updated on STN: 20030222
Entered Medline: 20030221

AB Proteins of the ARGONAUTE family are important in diverse posttranscriptional RNA-mediated gene-silencing systems as well as in transcriptional gene silencing in Drosophila and fission yeast and in programmed DNA elimination in Tetrahymena. We cloned ARGONAUTE4 (AGO4) from a screen for mutants that suppress silencing of the Arabidopsis SUPERMAN (SUP) gene. The ago4-1 mutant reactivated silent SUP alleles and decreased CpNpG and asymmetric DNA methylation as well as histone H3 lysine-9 methylation. In addition, ago4-1 blocked histone and DNA methylation and the accumulation of 25-nucleotide small interfering RNAs (siRNAs) that correspond to the retroelement AtSN1. These results suggest that AGO4 and long siRNAs direct chromatin modifications, including histone methylation and non-CpG DNA methylation.

L9 ANSWER 16 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2003016379 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12486103
TITLE: The PAAD/PYRIN-family protein ASC is a dual regulator of a conserved step in nuclear factor kappaB activation pathways.
AUTHOR: Stehlik Christian; Fiorentino Loredana; Dorfleutner Andrea; Bruey Jean-Marie; Ariza Eugenia M; Sagara Junji; Reed John C
CORPORATE SOURCE: The Burnham Institute, The Scripps Research Institute, La Jolla, CA 92037, USA.
SOURCE: Journal of experimental medicine, (2002 Dec 16) 196 (12) 1605-15.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200302
ENTRY DATE: Entered STN: 20030114
Last Updated on STN: 20030212
Entered Medline: 20030211

AB Apoptosis-associated speck-like protein containing a Caspase recruitment domain (ASC) belongs to a large family of proteins that contain a Pyrin, AIM, ASC, and death domain-like (PAAD) domain (also known as PYRIN, DAPIN, Pyk). Recent data have suggested that ASC functions as an adaptor protein linking various PAAD-family proteins to pathways involved in nuclear factor (NF)-kappaB and pro-Caspase-1 activation. We present evidence here that the role of ASC in modulating NF-kappaB activation pathways is much broader than previously suspected, as it can either inhibit or activate NF-kappaB, depending on cellular context. While coexpression of ASC with certain PAAD-family proteins such as Pyrin and Cryopyrin increases NF-kappaB activity, ASC has an inhibitory influence on NF-kappaB activation by various proinflammatory stimuli, including tumor necrosis factor (TNF)alpha, interleukin 1beta, and lipopolysaccharide (LPS). Elevations in ASC protein levels or of the PAAD domain of ASC suppressed activation of IkappaB kinases in cells exposed to pro-inflammatory stimuli. Conversely, reducing endogenous levels of ASC using siRNA enhanced TNF- and LPS-induced degradation of the IKK substrate, IkappaBalpha. Our findings suggest that ASC modulates diverse NF-kappaB induction pathways by acting upon the IKK complex, implying a broad role for this and similar proteins containing PAAD domains in regulation of inflammatory responses.

L9 ANSWER 17 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2002272620 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12011447
TITLE: ARGONAUTE1 is required for efficient RNA interference in Drosophila embryos.
AUTHOR: Williams Robert W; Rubin Gerald M
CORPORATE SOURCE: Department of Molecular and Cell Biology and the Howard Hughes Medical Institute, University of California, Berkeley, CA 94720-3200, USA.. bobby@fruitfly.org
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2002 May 14) 99 (10) 6889-94. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020516
Last Updated on STN: 20021211
Entered Medline: 20020618

AB Double-stranded RNA (dsRNA) triggers homology-dependent posttranscriptional gene interference (RNAi) in a diverse range of eukaryotic organisms, in a process mechanistically related to viral and transgene-mediated cosuppression. RNAi is characterized by the conversion of long dsRNA into approximately 21-25-nt small interfering RNAs (siRNA) that guide the degradation of homologous mRNA. Many of the genes required for siRNA production and target mRNA degradation are widely conserved. Notably, members of the Argonaute-like gene family from Arabidopsis, Caenorhabditis elegans, Drosophila, and Neurospora have been genetically and/or biochemically identified as components of the RNAi/cosuppression pathway. We show here that mutations in the Drosophila Argonaute1 (AGO1) gene suppress RNAi in embryos. This defect corresponds to a reduced ability to degrade mRNA in response to dsRNA in vitro. Furthermore, AGO1 is not required for siRNA production in vitro nor can the introduction of siRNA bypass AGO1 mutants in vivo. These data suggest that AGO1 functions downstream of siRNA production.

L9 ANSWER 18 OF 49 MEDLINE on STN
ACCESSION NUMBER: 2002243515 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11981565
TITLE: Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells.
COMMENT: Comment in: Nat Biotechnol. 2002 May;20(5):446-8. PubMed ID: 11981553
Comment in: Nat Biotechnol. 2003 Mar;21(3):230-1. PubMed ID: 12610564
AUTHOR: Lee Nan Sook; Dohjima Taikoh; Bauer Gerhard; Li Haitang; Li Ming-Jie; Ehsani Ali; Salvaterra Paul; Rossi John
CORPORATE SOURCE: Division of Molecular Biology, Graduate School of Biological Sciences, City of Hope, Duarte, CA 91010, USA.
CONTRACT NUMBER: AI 29329 (NIAID)
AI 46030 (NIAID)
AI42552 (NIAID)
SOURCE: Nature biotechnology, (2002 May) 20 (5) 500-5. Journal code: 9604648. ISSN: 1087-0156.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020501

Last Updated on STN: 20020906
Entered Medline: 20020905

AB RNA interference (RNAi) is the process of sequence-specific, posttranscriptional gene silencing in animals and plants initiated by double-stranded (ds) RNA that is homologous to the silenced gene. This technology has usually involved injection or transfection of dsRNA in model nonvertebrate organisms. The longer dsRNAs are processed into short (19 25 nucleotides) small interfering RNAs (siRNAs) by a ribonucleotide protein complex that includes an RNAse III related nuclease (Dicer), a helicase family member, and possibly a kinase and an RNA-dependent RNA polymerase (RdRP). In mammalian cells it is known that dsRNA 30 base pairs or longer can trigger interferon responses that are intrinsically sequence-nonspecific, thus limiting the application of RNAi as an experimental and therapeutic agent. Duplexes of 21-nucleotide siRNAs with short 3' overhangs, however, can mediate RNAi in a sequence-specific manner in cultured mammalian cells. One limitation in the use of siRNA as a therapeutic reagent in vertebrate cells is that short, highly defined RNAs need to be delivered to target cells--a feat thus far only accomplished by the use of synthetic, duplex RNAs delivered exogenously to cells. In this report, we describe a mammalian Pol III promoter system capable of expressing functional double-stranded siRNAs following transfection into human cells. In the case of the 293 cells cotransfected with the HIV-1 pNL4-3 proviral DNA and the siRNA-producing constructs, we were able to achieve up to 4 logs of inhibition of expression from the HIV-1 DNA.

L9 ANSWER 19 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:168116 BIOSIS
DOCUMENT NUMBER: PREV200400162022
TITLE: Biological effects on PBL of PTPN6 gene silencing by siRNA.
AUTHOR(S): Mena-Duran, Armando V. [Reprint Author]; Togo, Summanuna [Reprint Author]; Mustelin, Tomas [Reprint Author]
CORPORATE SOURCE: Signal Transduction, Burnham Institute, La Jolla, CA, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 167b. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2004
Last Updated on STN: 24 Mar 2004

AB PTPN6 gene is located in chromosome 12p13 and codes for a 68 kD protein (SHP-1) member of the protein -tyrosine-phosphatases family. The viable motheaten (Hcph(me-v)) mice are deficient in SHP-1 protein-tyrosine phosphatase and show severe hematopoeisis aberrations. SHP-1 expression errors like RNA aberrant splicing, null expression or promoter methylation have been reported in different leukemias and lymphomas. SHP-1 is known as a repressor of cytokine signaling and it's involved in many cell functions, from hematopoetic cell development to cell signaling. In normal resting lymphocytes is constitutively expressed and has roles as a negative repressor of BCR signaling for proliferation and apoptosis. In stimulated B lymphocytes forms a complex with CD22 and Lyn that downregulate BCR signaling. TCR is also regulated by SHP-1 affecting thymocyte selection and TCR driven apoptosis. In mice deficient models, T cells also showed enhanced Fas ligand expression and activation induced cell death. TCR trigger threshold is also modulated by SHP-1. Although associated with CTLA4 and CD22 there's no evidence that SHP-1 modulates their TCR

inhibiting functions. But there are evidences on how SHP-1 interacts with CD5 and enhances its activity on CD3, ZAP70, Syk, and PLC 1. SHP-1 also has effects on PTK functions. SHP-1 has been shown to downregulate TCR-induced activation of Src-family PTKs, such as Lck and Fyn82. What effects will we expect if PTPN6 gene expression were transiently silenced by siRNA in mature PBL? To address this question we designed 21 bp siRNAs and tested it on PBL obtained from buffy coat of healthy donors purchased from San Diego Blood Bank. Lymphocytes were transfected using Nucleofector(R) (Amaxa, Germany) and cultured in complete RPMI medium and stimulated by IL-2 pulses (100 U/mL) every 24 hrs. G3BP siRNA transfected lymphocytes were used as controls. Cells were harvested every 24 hrs till 96 hrs after starting culture. Cells were lysed and protein concentration was measured by BCA protein assay (Pierce, Rockford, IL). Lysates were electrophoresed in a SDS-PAGE and blotted against SHP-1 antibody (Santa Cruz Biotech, Santa Cruz, CA). For morphological studies, cells were stained by May-Grunwald Giemsa. For studies on proliferation, cells were counted in a Neubauer chamber after Trypan blue exclusion test and using colorimetric test Cell titer 96 Aqueous One solution (Promega, Madison, WI). Cell cycle was studied by PI staining and flow cytometry. Confocal microscopy was used for immunofluorescence studies. PTPN6 was efficiently silenced using two differently designed iRNAs as verified by WB. Gene silencing is more apparent after 48 hrs of transfection on performed WB but some background activity is always found. Surprisingly, proliferation assays showed no difference between transfected cells and controls stimulated with PHA and IL-2. Cell cycle analysis is also being tested to look for proliferative advantage of siRNA transfected PBL. To our knowledge, we show for the first time ever, spatial disappearance of SHP-1 after siRNA transfection, with immunofluorescence confocal microscopy on PBL. Concluding, PTPN6 gene silencing is feasible with siRNA technology on PBL but it's far from being effective on every cultured cell. Cell viability is seriously affected. Translational interference of SHP-1 by siRNA does not confer a proliferation advantage or immortalization, at least, in mature lymphocytes.

L9 ANSWER 20 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:150988 BIOSIS
DOCUMENT NUMBER: PREV200400147270
TITLE: CD13/APN transcription is induced by Ras/MapK mediated phosphorylation of Ets-2 in activated endothelial cells.
AUTHOR(S): Petrovic, Nenad [Reprint Author]; Bhagwat, Shripad V.; Ratzan, William J. [Reprint Author]; Ostrowski, Michael C.; Shapiro, Linda H. [Reprint Author]
CORPORATE SOURCE: Center for Vascular Biology, University of Connecticut Health Center, Farmington, CT, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 532a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB In the resting endothelial cells of mature blood vessels the CD13/aminopeptidase N (CD 13/APN) cell surface peptidase is transcriptionally inactive, but its expression is highly induced on the endothelium of newly forming vessels activated in response to angiogenic stimuli such as hypoxia and angiogenic growth factors. We have previously

shown that CD13/APN induction by angiogenic growth factor signals is mediated via the Ras/MapK pathway. Enforced expression of CD13/APN can overcome the block to angiogenesis resulting from treatment with inhibitors of this pathway, indicating that CD13/APN is a key target of angiogenic signal transduction. Furthermore, functional CD13/APN is necessary for certain endothelial cell functions, and inhibition of CD13/APN peptidase activity halts angiogenesis both in vitro and in vivo. To extend our investigation of intracellular regulators of angiogenesis, we have explored the nuclear effectors downstream of the Ras/MapK pathway that are responsible for CD13/APN induction. The response to serum/angiogenic growth factor signals mapped to a 38 bp region of the CD13/APN proximal promoter containing an Ets-family core motif that specifically binds a protein complex in nuclear lysates prepared from activated endothelial cells. This motif and the proteins that target it are functionally relevant since mutation of this sequence in the context of the intact promoter abrogates CD13/APN transcription in endothelial cells. To identify the specific Ets family member controlling CD13/APN transcription, we analyzed a panel of endothelial cell expressed Ets family members and found that Ets-2 expression plasmids, and to a lesser extent Ets-1, each transactivate CD13/APN promoter activity via the Ets-core motif, while plasmids encoding Fli, Erg, and NERF family members are inactive. Because Ets-2 is a well characterized phosphorylation target of the Erk1/2 kinase in fibroblasts, we investigated if the induction of CD13/APN by serum is mediated by phosphorylation of Ets-2 via Ras/MapK in endothelial cells. Western blot analysis of lysates from activated endothelial cells showed that Ets-2 is phosphorylated in an Erk1/2 dependent fashion, verifying that this mechanism is operative in endothelial cells. Transactivation assays using a phosphorylation-defective Ets-2 mutant expression plasmid showed that the mutated protein failed to stimulate CD13/APN transcription, indicating that Ets-2 phosphorylation is obligatory for CD13/APN induction. To confirm a role for endogenous Ets-2 in the endothelial cell expression of CD13/APN, we specifically abrogated Ets-2 mRNA and protein by siRNA duplexes directed toward Ets-2 sequences, resulting in complete abrogation of CD13/APN transactivation by exogenously added Ets-2 and a dose dependent decrease in CD13/APN promoter activity driven by endogenous Ets-2. Finally, to assess the relevance of Ets-2 in endothelial cell function, we induced capillary network formation by plating endothelial cells containing Ets-2 siRNA oligonucleotides on Matrigel basement membrane matrix preparations. Cells containing inhibitory, but not inactive. siRNAs were completely incapable of forming the organized networks characteristic of differentiating endothelial cells, confirming that Ets-2 is required for endothelial morphogenesis. Thus, the phosphorylation of Ets-2 by Erk is a prerequisite for CD13/APN transcriptional induction in endothelial cells, and functional Ets-2 and its targets play essential roles in endothelial cell function.

L9 ANSWER 21 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:568619 BIOSIS
DOCUMENT NUMBER: PREV200300563479
TITLE: MYELOID CELL LEUKEMIA (MCL)-1 PROTEIN MEDIATES APOPTOSIS RESISTANCE IN CHOLANGIOCYTES.
AUTHOR(S): Taniai, Makiko [Reprint Author]; Higuchi, Hajime [Reprint Author]; Bronk, Steven F. [Reprint Author]; Gores, Gregory J. [Reprint Author]
CORPORATE SOURCE: Rochester, MN, USA
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. S930. e-file. Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society

for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Dec 2003
Last Updated on STN: 3 Dec 2003

AB Cholangiocytes and their transformed counterpart, cholangiocarcinomas, express high levels of antiapoptotic proteins and are resistant to apoptosis. In particular, these cells richly express Mcl-1, a potent antiapoptotic protein of the Bcl-2 family. Thus, our AIMS were to test the hypothesis that Mcl-1 is responsible for the resistance of cholangiocytes and cholangiocarcinoma cells to apoptosis. We choose TNF-alpha related apoptosis inducing ligand (TRAIL) to induce apoptosis as this death ligand is expressed by natural killer cells and likely participates in immune mediated bile duct injury, and it is being evaluated as a chemotherapeutic agent for human malignancies. METHODS: Cholangiocytes were isolated from sham operated and two week bile duct ligated (BDL) mice. KMCH cells were used as representative human cholangiocarcinoma cell line. Mcl-1 expression was examined using real time PCR technology and immunoblot analysis. KMCH cells were stably transfected with small interfering RNA (siRNAs) construct to knock down Mcl-1 expression, KMCH-siRNA. Human recombinant Flag tagged TRAIL pre-oligomerized with M2 antisera was used to induce apoptosis. Apoptosis was quantitated using the fluorescent dye DAPI and fluorescence microscopy. Caspase activity was quantitated using CaspaTag and fluorescence microscopy. RESULTS: Mcl-1 mRNA expression in cholangiocytes from BDL mice was 100-fold greater than in cholangiocytes from sham-operated animals. The enhanced Mcl-1 expression in cholangiocytes from BDL mice was confirmed by immunoblot analysis. TRAIL induced apoptosis was reduced in choalngiocytes from BDL animals vs sham operated mice. Having confirmed that Mcl-1 regulates TRAIL sensitivity in primary cells, we next evaluated the role of Mcl-1 in KMCH cells treated with TRAIL. These cells richly express Mcl-1; however, Mcl-1 expression was reduced 80% in the KMCH-siRNA cells as compared to the parent cells by immunoblot analysis. TRAIL-induced apoptosis was 3-fold greater in the KMCH-siRNA vs. mock transfected cells. Caspase activity paralleled the morphologic quantitative assessment of apoptosis. In CONCLUSION, these data indicate that Mcl-1 is a potent anti-apoptotic protein in cholangiocytes and cholangiocarinoma cells. Up regulation of Mcl-1 occurs in proliferating bile duct cells following BDL suggesting a role for this protein in bile duct proliferation. Down regulation of Mcl-1 expression may be a potential therapeutic strategy for the treatment of cholangiocarcinoma..

L9 ANSWER 22 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:539131 BIOSIS
DOCUMENT NUMBER: PREV200300541504
TITLE: The armadillo family protein p120 modulates cadherin expression by regulating cadherin internalization and degradation.
AUTHOR(S): Kowalczyk, A. P. [Reprint Author]; Xiao, K. [Reprint Author]; Allison, D. F. [Reprint Author]; Kottke, M. D. [Reprint Author]; Summers, S. [Reprint Author]; Vincent, P. A.; Faundez, V.
CORPORATE SOURCE: Dermatology, Emory University, Atlanta, GA, USA
SOURCE: Journal of Investigative Dermatology, (July 2003) Vol. 121, No. 1, pp. 0300. print.
Meeting Info.: International Investigative Dermatology 2003 : Joint Meeting of the European Society for Dermatological Research, Japanese Society for Investigative Dermatology and Society for Investigative Dermatology. Miami Beach, Florida, USA. April 30-May 04, 2003. European Society for

Dermatological Research.
ISSN: 0022-202X (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003

L9 ANSWER 23 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:502973 BIOSIS
DOCUMENT NUMBER: PREV200300498635
TITLE: The PAAD/PYRIN-family protein ASC/TMS1 is a dual regulator of a conserved step in NF-kappaB activation.
AUTHOR(S): Stehlik, Christian [Reprint Author]; Fiorentino, Loredana; Dorfleutner, Andrea; Sagara, Junji; Reed, John C.
CORPORATE SOURCE: Burnham Institute, La Jolla, CA, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 1190. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003

L9 ANSWER 24 OF 49 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:356987 BIOSIS
DOCUMENT NUMBER: PREV200300356987
TITLE: The PAAD/PYRIN-Family Protein ASC Is a Regulator of a Conserved Step in NF-kB Activation Pathways.
AUTHOR(S): Stehlik, Christian [Reprint Author]; Fiorentino, Loredana [Reprint Author]; Dorfleutner, Andrea [Reprint Author]; Ariza, Eugenia M. [Reprint Author]; Sagara, Junji [Reprint Author]; Reed, John C. [Reprint Author]
CORPORATE SOURCE: The Burnham Institute, La Jolla, CA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 2853. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 18 Sep 2003
AB ASC ("Apoptosis-associated speck-like protein containing a Caspase recruitment domain") is a bipartite protein containing both a CARD and a PAAD/PYRIN domain. Recent data have suggested that ASC functions as an adapter protein linking various PAAD-family proteins to pathways involved in NF-kB and pro-Caspase-1 activation. We present evidence here that the role of ASC in modulating NF-kB activation pathways is much broader than previously suspected, as it can either inhibit or enhance NF-kB, depending on cellular context. While co-expression of ASC with certain PAAD-family proteins such as Pyrin and Cryopyrin synergistically increases NF-kB activity, ASC has an inhibitory influence

on NF-kB activation by various pro-inflammatory stimuli, including TNFa, IL-1b, and LPS, as measured by NF-kB reporter-gene assays, analysis of expression of NF-kB-responsive genes ICAM and TRAF 1, and by electro-mobility shift assays (EMSA). Gene transfer-mediated increases in full-length ASC or of a mutant containing only the PAAD/PRYIN domain suppressed activation of IkB kinases (IKKs) in cells exposed to pro-inflammatory stimuli, as measured by in vitro kinase assays and immunoblotting using phospho-specific antibodies. Conversely, reducing endogenous levels of ASC using siRNA enhanced TNFa- and LPS-induced degradation of the IKK substrate, IkBa. Using co-immunoprecipitation assays, we also observed association of endogenous ASC with the IKK complex, suggesting direct regulation of this kinase complex involved in triggering IkB degradation, thereby releasing NF-kB. Our findings thus suggest that ASC modulates diverse NF-kB-induction pathways by acting upon the IKK complex, implying a broad role for this and similar proteins containing PAAD/PYRIN domains in regulation of inflammatory responses.

L9 ANSWER 25 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1005984 CAPLUS
DOCUMENT NUMBER: 142:232153
TITLE: Strategy for siRNA-based gene therapy of SARS
AUTHOR(S): Meng, Xia; Hu, Fang; Qiu, Qihong; Ye, Xun; Liang, Min; Chen, Hongzhuan
CORPORATE SOURCE: Dept of Pharmacology, Shanghai Second Medical University, Shanghai, 200025, Peop. Rep. China
SOURCE: Zhongguo Yaolixue Tongbao (2003), 19(7), 723-726
CODEN: ZYTOE8; ISSN: 1001-1978
PUBLISHER: Anhui Yike Daxue Linchuan Yaoli Yanjiuso
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review with 23 refs. on strategy for siRNA-based gene therapy of SARS with subdivision headings: (1) the coronavirus family and coronavirus causing severe acute respiratory syndrome; (2) the drugs for treating SARS; (3) siRNA drugs and (4) strategy for siRNA based gene therapy of SARS.

L9 ANSWER 26 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:835858 CAPLUS
DOCUMENT NUMBER: 140:37505
TITLE: Functional genomics in Xenopus laevis: Towards transgene-driven RNA interference and cell-specific transgene expression
AUTHOR(S): Dirks, Ron P. H.; Bouw, Gerrit; Van Huizen, Rick; Jansen, Eric J. R.; Martens, Gerard J. M.
CORPORATE SOURCE: Department of Molecular Animal Physiology, Nijmegen Center for Molecular Life Sciences (NCMLS), University of Nijmegen, Nijmegen, 6525 GA, Neth.
SOURCE: Current Genomics (2003), 4(8), 699-711
CODEN: CGUEA8; ISSN: 1389-2029
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The most direct approach to study the physiol. role of a protein of unknown function (Functional Genomics) is to change its expression pattern in an intact organism and analyze the phenotypic consequences of this manipulation. The introduction of a method to generate stably transgenic Xenopus laevis has paved the way to the use of tissue/cell- and developmental stage-specific promoters allowing to study the physiol. function of proteins in a defined set of fully differentiated cells. Whereas stable (over)expression of proteins in Xenopus is now within reach, stable inhibition of protein expression can only be

accomplished randomly, by gene trap approaches. We here report our efforts to induce stable RNA interference (RNAi) in X. laevis via transgene-driven expression of inverted repeats. Stable, and muscle- and neuron-specific knock-down of expression of exogenous green fluorescent protein (GFP) reporter was achieved via RNA polymerase II promoter-driven expression of long GFP RNA duplexes. Unfortunately, our attempts to induce RNAi directed against various endogenous targets, based on the use of RNA polymerase II and III promoters, and long and short inverted repeats have not resulted in a reliable protocol for stable, transgene-driven RNAi in Xenopus. In the second part, we present an example of the use of a cell-specific promoter for functional studies. Cell-specific transgene overexpression of a GFP-tagged member of the p24 family thought to be involved in intracellular protein transport was achieved and this manipulation of the intermediate pituitary melanotrope cell had a phenotypic consequence at its physiol. target, the skin melanophore. Thus, the traditional exptl. advantages of X. laevis combined with the recently developed technique of stable, non-mosaic Xenopus transgenesis make this lower vertebrate an attractive model organism for Functional Genomics.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 27 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:835669 CAPLUS

DOCUMENT NUMBER: 139:376780

TITLE: HdmX stimulates Hdm2-mediated ubiquitination and degradation of p53

AUTHOR(S): Linares, Laetitia K.; Hengstermann, Arnd; Ciechanover, Aaron; Mueller, Stefan; Scheffner, Martin

CORPORATE SOURCE: Center for Biochemistry, Medical Faculty, University of Cologne, Cologne, 50931, Germany

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2003), 100(21), 12009-12014 CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The RING finger proteins HdmX and Hdm2 share significant structural and functional similarity. Hdm2 is a member of the RING finger family of ubiquitin-protein ligases E3 and targets the tumor suppressor protein p53 for degradation Although HdmX also binds to p53, HdmX does not induce p53 degradation Moreover, HdmX has been reported to interfere with p53 degradation in overexpression expts. To obtain insight into the mechanism by which HdmX interferes with p53 degradation, we studied the effect of HdmX on the E3 activity of Hdm2 in vitro. Surprisingly, this revealed that HdmX stimulates Hdm2-mediated ubiquitination of p53 and that HdmX facilitates ubiquitination of Hdm2 and vice versa. In addition, down-regulation of HdmX expression within cells results in the accumulation of both p53 and Hdm2. Because HdmX alone does not have appreciable E3 activity, these data indicate that HdmX acts as a stimulator, rather than as an inhibitor, of the E3 activity of Hdm2 and that, at least under certain conditions, HdmX is actively involved in the degradation of both p53 and Hdm2.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 28 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:434595 CAPLUS

DOCUMENT NUMBER: 139:32331

TITLE: Protein-protein interactions involved in signaling by transforming growth factor-β or TGFβ family members and uses thereof

INVENTOR(S): Legrain, Pierre; Gauthier, Jean-Michel; Colland, Frederic; Jacq, Xavier
PATENT ASSIGNEE(S): Hybrigenics, Fr.
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003045990 A2		20030605	WO 2002-EP13866	20021126

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR

PRIORITY APPLN. INFO.: US 2001-PV333348 20011126
US 2002-PV384537 20020531
US 2002-PV422471 20021030

AB The present invention relates to protein-protein interactions involved in transforming growth factor-β (TGFβ) disorders and/or diseases. More specifically, the present invention relates to complexes of polypeptides or polynucleotides encoding the polypeptides, fragments of the polypeptides, Selected Interacting Domains (SID®) which are identified due to the protein-protein interactions, methods for screening drugs for agents which modulate the interaction of proteins, and pharmaceutical compns. that are capable of modulating the protein-protein interactions. The invention claims polynucleotide and polypeptide sequences for SID® proteins. Some examples show effects of siRNA downregulation or overexpression of SID proteins on TGFβ- and bone morphogenetic protein-dependent reporter activity.

L9 ANSWER 29 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:417896 CAPLUS
DOCUMENT NUMBER: 139:2123
TITLE: cDNA and proteins sequences for ATRIP (ATR-interacting protein) and uses in cell cycle checkpoint signaling
INVENTOR(S): Elledge, Stephen J.; Cortez, David. K.; Lee, Zou
PATENT ASSIGNEE(S): Baylor College of Medicine, USA
SOURCE: PCT Int. Appl., 172 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003044214	A2	20030530	WO 2002-US37133	20021120
WO 2003044214	A3	20031127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,

CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003165934 A1 20030904 US 2002-300453 20021120

PRIORITY APPLN. INFO.: US 2001-331821P P 20011120

AB The invention claims nucleic acid and polypeptide sequences for human protein ATRIP (ATR-interacting protein). ATRIP was identified as an interactor with ATR, a member of the phosphatidylinositol kinase-related protein family that includes ATM and DNA-PK. In some embodiments, the present invention is directed to ATRIP and ATR acting as mutually dependent partners in cell cycle checkpoint signaling pathways. The invention claims compns. and methods for diagnosis and treatment of ATRIP gene and polypeptide mutations and for identification of agents which modulate ATRIP function as it relates to signaling for the presence of DNA damage or replication stress and activating cell cycle checkpoints. The inventions also claims methods for identification and use of cell proliferation, cell death, and cancer agents which are derived from ATRIP or ATRIP complexes with ATR kinase, ssDNA/RPA (replication protein A), or phosphoproteins. ATRIP protein expression is dependent on ATR kinase gene expression. and reduction of ATRIP expression by siRNA also results in less ATR protein expression. Loss of expression of both ATR and ATRIP genes results in a γ-irradiation-induced G2-M checkpoint defect. SsDNA-bound recombinant human RAD17 is phosphorylated by the ATR/ATRIP complex in an RPA-dependent reaction. ATRIP is considered the functional human homolog of the RAD26 gene family.

L9 ANSWER 30 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:300152 CAPLUS

DOCUMENT NUMBER: 139:111979

TITLE: Cdc42 is a Rho GTPase family member that can mediate insulin signaling to glucose transport in 3T3-L1 adipocytes

AUTHOR(S): Usui, Isao; Imamura, Takeshi; Huang, Jie; Satoh, Hiroaki; Olefsky, Jerrold M.

CORPORATE SOURCE: Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Diego, La Jolla, CA, 92093-0673, USA

SOURCE: Journal of Biological Chemistry (2003), 278(16), 13765-13774
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors investigated the role of cdc42, a Rho GTPase family member, in insulin-induced glucose transport in 3T3-L1 adipocytes. Microinjection of anti-cdc42 antibody or cdc42 siRNA led to decreased insulin-induced and constitutively active Gq (CA-Gq; Q209L)-induced GLUT4 translocation. Adenovirus-mediated expression of constitutively active cdc42 (CA-cdc42; V12) stimulated 2-deoxyglucose uptake to 56% of the maximal insulin response, and this was blocked by treatment with the phosphatidylinositol 3-kinase (PI3-kinase) inhibitor, wortmannin, or LY294002. Both insulin and CA-Gq expression caused an increase in cdc42 activity, showing that cdc42 is activated by insulin and is downstream of Gαq/11 in this activation pathway. Immunopptn. expts. showed that insulin enhanced a direct association of cdc42 and p85, and both insulin treatment and CA-cdc42 expression stimulated PI3-kinase activity in immunoppts. with anti-cdc42 antibody. Furthermore, the effects of insulin, CA-Gq, and CA-cdc42 on GLUT4 translocation or 2-deoxyglucose uptake were inhibited by microinjection of anti-protein kinase Cλ (PKCλ) antibody or overexpression of a kinase-deficient PKCλ construct. In summary, activated cdc42 can mediate insulin-stimulated GLUT4 translocation and glucose transport in a PI3-kinase-dependent manner. Insulin treatment and constitutively active Gq expression can enhance the cdc42 activity state as well as the association of cdc42 with

activated PI3-kinase. (4) PKCλ inhibition blocks CA-cdc42, CA-Gq, and insulin-stimulated GLUT4 translocation. Taken together, these data indicate that cdc42 can mediate insulin signaling to GLUT4 translocation and lies downstream of Gαq/11 and upstream of PI3-kinase and PKCλ in this stimulatory pathway.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 31 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:89294 CAPLUS
DOCUMENT NUMBER: 139:20080
TITLE: POSH acts as a scaffold for a multiprotein complex that mediates JNK activation in apoptosis
AUTHOR(S): Xu, Zhiheng; Kukekov, Nickolay V.; Greene, Lloyd A.
CORPORATE SOURCE: Department of Pathology, Columbia University, College of Physicians and Surgeons, Center for Neurobiology and Behavior, New York, NY, 10032, USA
SOURCE: EMBO Journal (2003), 22(2), 252-261
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We report that the multidomain protein POSH (plenty of SH3s) acts as a scaffold for the JNK pathway of neuronal death. This pathway consists of a sequential cascade involving activated Rac1/Cdc42, mixed-lineage kinases (MLKs), MAP kinase kinases (MKKs) 4 and 7, c-Jun N-terminal kinases (JNKs) and c-Jun, and is required for neuronal death induced by various means including nerve growth factor (NGF) deprivation. In addition to binding GTP-Rac1 as described previously, we find that POSH binds MLKs both in vivo and in vitro, and complexes with MKKs 4 and 7 and with JNKs. POSH overexpression promotes apoptotic neuronal death and this is suppressed by dominant-neg. forms of MLKs, MKK4/7 and c-Jun, and by an MLK inhibitor. Moreover, a POSH antisense oligonucleotide and a POSH small interfering RNA (siRNA) suppress c-Jun phosphorylation and neuronal apoptosis induced by NGF withdrawal. Thus, POSH appears to function as a scaffold in a multiprotein complex that links activated Rac1 and downstream elements of the JNK apoptotic cascade.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 32 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:589838 CAPLUS
DOCUMENT NUMBER: 137:307346
TITLE: Endogenous and silencing-associated small RNAs in plants
AUTHOR(S): Llave, Cesar; Kasschau, Kristin D.; Rector, Maggie A.; Carrington, James C.
CORPORATE SOURCE: Center for Gene Research and Biotechnology, Oregon State University, Corvallis, OR, 97331, USA
SOURCE: Plant Cell (2002), 14(7), 1605-1619
CODEN: PLCEEW; ISSN: 1040-4651
PUBLISHER: American Society of Plant Biologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A large set of endogenous small RNAs of predominantly 21 to 24 nucleotides was identified in Arabidopsis. These small RNAs resembled micro-RNAs from animals and were similar in size to small interfering RNAs that accumulated during RNA silencing triggered by multiple types of inducers. Among the 125 sequences identified, the vast majority (90%) arose from intergenic regions, although small RNAs corresponding to predicted protein-coding genes, transposon-like sequences, and a structural RNA gene also were identified. Evidence consistent with the derivation of small RNAs of both polarities, and from highly base-paired precursors, was

obtained through the identification and anal. of clusters of small RNA loci. The accumulation of specific small RNAs was regulated developmentally. The authors propose that Arabidopsis small RNAs participate in a wide range of post-transcriptional and epigenetic events.
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 33 OF 49 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:5025 CAPLUS
DOCUMENT NUMBER: 136:397677
TITLE: Biosynthesis of the linkage region of glycosaminoglycans. Cloning and activity of galactosyltransferase II, the sixth member of the β1,3-galactosyltransferase family (β3GalT6)
AUTHOR(S): Bai, Xiaomei; Zhou, Dapeng; Brown, Jillian R.; Crawford, Brett E.; Hennet, Thierry; Esko, Jeffrey D.
CORPORATE SOURCE: Department of Cellular and Molecular Medicine, Glycobiology Research and Training Center, University of California, San Diego, La Jolla, CA, 92093-0687, USA
SOURCE: Journal of Biological Chemistry (2001), 276(51), 48189-48195
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A family of five β1,3-galactosyltransferases has been characterized that catalyze the formation of Galβ1, 3GlcNAcβ and Galβ1,3GalNAcβ linkages present in glycoproteins and glycolipids (β3GalT1, -2, -3, -4, and -5). We now report a new member of the family (β3GalT6), involved in glycosaminoglycan biosynthesis. The human and mouse genes were located on chromosomes 1p36.3 and 4E2, resp., and homologs are found in Drosophila melanogaster and Caenorhabditis elegans. Unlike other members of the family, β3GalT6 showed a broad mRNA expression pattern by Northern blot anal. Although a high degree of homol. across several subdomains exists among other members of the β3-galactosyltransferase family, recombinant enzyme did not utilize glucosamine- or galactosamine-containing acceptors. Instead, the enzyme transferred galactose from UDP-galactose to acceptors containing a terminal β-linked galactose residue. This product, Galβ1,3Galβ is found in the linkage region of heparan sulfate and chondroitin sulfate (GlcAβ1;3Galβ1,3Galβ1,4Xylβ-O-Ser), indicating that β3GalT6 is the so-called galactosyltransferase II involved in glycosaminoglycan biosynthesis. Its identity was confirmed in vivo by siRNA-mediated inhibition of glycosaminoglycan synthesis in HeLa S3 cells. Its localization in the medial Golgi indicates that this is the major site for assembly of the linkage region.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 34 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004124711 EMBASE
TITLE: Chemosensitivity linked to p73 function.
AUTHOR: Irwin M.S.; Kondo K.; Marin M.C.; Cheng L.S.; Hahn W.C.; Kaelin Jr. W.G.
CORPORATE SOURCE: W.G. Kaelin Jr., Dana-Farber Cancer Institute, Brigham and Womens Hospital, Harvard Medical School, 44 Binney Street, Boston, MA 02115, United States.
william_kaelin@dfci.harvard.edu
SOURCE: Cancer Cell, (2003) 3/4 (403-410).
Refs: 42

ISSN: 1535-6108 CODEN: CCAECI
PUBLISHER IDENT.: S 1535-6108(03)00078-3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Most chemotherapeutic agents induce DNA damage, leading to p53 accumulation and apoptosis. The factors that determine chemosensitivity in p53-defective tumor cells are poorly understood. We found that the p53 family member p73 is induced by a wide variety of chemotherapeutic drugs. Blocking p73 function with a dominant-negative mutant, siRNA, or homologous recombination led to chemoresistance of human tumor cells and engineered transformed cells, irrespective of p53 status. Mutant p53 can inactivate p73 and downregulation of mutant p53 enhanced chemosensitivity. These findings indicate that p73 is a determinant of chemotherapeutic efficacy in humans.

L9 ANSWER 35 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003489016 EMBASE
TITLE: Suppression of the dual-specificity phosphatase MKP-1 enhances HIF-1 trans-activation and increases expression of EPO.
AUTHOR: Liu C.; Shi Y.; Han Z.; Pan Y.; Liu N.; Han S.; Chen Y.; Lan M.; Qiao T.; Fan D.
CORPORATE SOURCE: D. Fan, Institute of Digestive Diseases, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, Shaanxi Province, China. fandaim@fmmu.edu.cn
SOURCE: Biochemical and Biophysical Research Communications, (19 Dec 2003) 312/3 (780-786).
Refs: 39
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hypoxia-inducible factor 1 (HIF-1) is a phosphorylated protein and its phosphorylation is involved in HIF-1α subunit stabilization as well as in the regulation of HIF-1 transcriptional activity. In a variety of cell lines, the phosphorylation of HIF-1α is dependent on ERK or p38, two members of the mitogen-activated protein kinase (MAPK) superfamily. In addition, active MAPK could be inactivated through dephosphorylation by mitogen-activated protein kinase phosphatase-1 (MKP-1). MKP-1 has been identified as a hypoxia responsive gene, but its role in the response of cells to hypoxia is poorly understood. Here we found that hypoxia induces MKP-1 expression in human hepatoma cells HepG2 in a time-dependent manner. Inhibition of MKP-1 expression using siRNA technique could enhance HIF-1α phosphorylation, accompanied by an increase in transcriptionally active HIF-1 as well as a rise in the levels of HIF-1-induced erythropoietin expression. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L9 ANSWER 36 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003481168 EMBASE
TITLE: EndoPDI, a Novel Protein-disulfide Isomerase-like Protein That Is Preferentially Expressed in Endothelial Cells Acts as a Stress Survival Factor.
AUTHOR: Sullivan D.C.; Huminiecki L.; Moore J.W.; Boyle J.J.; Poulsom R.; Creamer D.; Barker J.; Bicknell R.

CORPORATE SOURCE: R. Bicknell, Molecular Angiogenesis Laboratory, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DS, United Kingdom. Roy.Bicknell@cancer.org.uk
SOURCE: Journal of Biological Chemistry, (21 Nov 2003) 278/47 (47079-47088).
Refs: 40
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We have identified a novel protein-disulfide isomerase and named it endothelial protein-disulfide isomerase (EndoPDI) because of its high expression in endothelial cells. Isolation of the full-length cDNA showed EndoPDI to be a 48 kDa protein that has three APWCGHC thioredoxin motifs in contrast to the two present in archetypal PDI. Ribonuclease protection and Western analysis has shown that hypoxia induces EndoPDI mRNA and protein expression. In situ hybridization analysis showed that EndoPDI expression is rare in normal tissues, except for keratinocytes of the hair bulb and syncytiotrophoblasts of the placenta, but was present in the endothelium of tumors and in other hypoxic lesions such as atherosclerotic plaques. We have compared the function of EndoPDI to that of PDI in endothelial cells using specific siRNA. PDI was shown to have a protective effect on endothelial cells under both normoxia and hypoxia. In contrast, EndoPDI has a protective effect only in endothelial cells exposed to hypoxia. The loss of EndoPDI expression under hypoxia caused a significant decrease in the secretion of adrenomedullin, endothelin-1, and CD105; molecules that protect endothelial cells from hypoxia-initiated apoptosis. The identification of an endothelial PDI further extends this increasing multigene family and EndoPDI, unlike archetypal PDI, may be a molecule with which to target tumor endothelium.

L9 ANSWER 37 OF 49 EMBASE
on STN
ACCESSION NUMBER: 2003473120 EMBASE
TITLE: A core function for p120-catenin in cadherin turnover.
AUTHOR: Davis M.A.; Ireton R.C.; Reynolds A.B.
CORPORATE SOURCE: A.B. Reynolds, Dept. of Cancer Biology, 771 PRB, 2220 Pierce Ave., Nashville, TN 37232-6840, United States. al.reynolds@mcmail.vanderbilt.edu
SOURCE: Journal of Cell Biology, (10 Nov 2003) 163/3 (525-534).
Refs: 47
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB p120-catenin stabilizes epithelial cadherin (E-cadherin) in SW48 cells, but the mechanism has not been established. Here, we show that p120 acts at the cell surface to control cadherin turnover, thereby regulating cadherin levels. p120 knockdown by siRNA expression resulted in dose-dependent elimination of epithelial, placental, neuronal, and vascular endothelial cadherins, and complete loss of cell-cell adhesion. ARVCF and δ-catenin were functionally redundant, suggesting that proper cadherin-dependent adhesion requires the presence of at least one p120 family member. The data reveal a core function of p120 in cadherin complexes, and strongly predict a dose-dependent loss of E-cadherin in tumors that partially or completely down-regulate p120.

L9 ANSWER 38 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003420065 EMBASE
TITLE: RNA interference and human disease.
AUTHOR: Cheng J.C.; Moore T.B.; Sakamoto K.M.
CORPORATE SOURCE: K.M. Sakamoto, Mattel Children's Hospital, David Geffen Sch. of Med. at UCLA, Los Angeles, CA 90095, United States. kms@ucla.edu
SOURCE: Molecular Genetics and Metabolism, (2003) 80/1-2 (121-128). Refs: 89
ISSN: 1096-7192 CODEN: MGMEFF
COUNTRY: United States
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The completion of the human genome project has left researchers searching for an efficient method to study gene function in mammalian cells. RNA interference (RNAi) is an evolutionarily conserved post-transcriptional gene silencing (PTGS) mechanism mediated by double-stranded RNA (dsRNA).The dsRNA is processed into small duplex RNA molecules of approximately 21-22 nucleotides (nts) termed small interfering RNAs (siRNAs) by a RNase III enzyme called Dicer. Interaction of siRNAs with a multi-protein complex, termed the RNA-induced silencing complex (RISC), results in sequence specific association of the activated RISC complex with the cognate RNA transcript (Fig. 1). This interaction leads to sequence-specific cleavage of the target transcript. Originally discovered in Caenorhabditis elegans, the study of RNAi in mammalian cells has blossomed in the last couple of years with the discovery that introduction of siRNA molecules directly into somatic mammalian cells circumvents the non-specific response vertebrate cells have against larger dsRNA molecules. Emerging as a powerful tool for reverse genetic analysis, RNAi is rapidly being applied to study the function of many genes associated with human disease, in particular those associated with oncogenesis and infectious disease. This review summarizes the mechanism of RNAi and provides an overview of its current applications in medicine.

L9 ANSWER 39 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003413402 EMBASE
TITLE: Differential contributions of condensin I and condensin II to mitotic chromosome architecture in vertebrate cells.
AUTHOR: Ono T.; Losada A.; Hirano M.; Myers M.P.; Neuwald A.F.; Hirano T.
CORPORATE SOURCE: T. Hirano, Cold Spring Harbor Laboratory, One Bungtown Road, Cold Spring Harbor, NY 11724, United States. hirano@cshl.org
SOURCE: Cell, (3 Oct 2003) 115/1 (109-121). Refs: 52
ISSN: 0092-8674 CODEN: CELLB5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The canonical condensin complex (henceforth condensin I) plays an essential role in mitotic chromosome assembly and segregation from yeast to humans. We report here the identification of a second condensin complex (condensin II) from vertebrate cells. Condensins I and II share the same pair of structural maintenance of chromosomes (SMC) subunits but contain

different sets of non-SMC subunits. siRNA-mediated depletion of condensin I- or condensin II-specific subunits in HeLa cells produces a distinct, highly characteristic defect in chromosome morphology. Simultaneous depletion of both complexes causes the severest defect. In Xenopus egg extracts, condensin I function is predominant, but lack of condensin II results in the formation of irregularly shaped chromosomes. Condensins I and II show different distributions along the axis of chromosomes assembled in vivo and in vitro. We propose that the two condensin complexes make distinct mechanistic contributions to mitotic chromosome architecture in vertebrate cells.

L9 ANSWER 40 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003300321 EMBASE
TITLE: Evidence that TRPC1 (transient receptor potential canonical 1) forms a Ca(2+)-permeable channel linked to the regulation of cell volume in liver cells obtained using small interfering RNA targeted against TRPC1.
AUTHOR: Chen J.; Barritt G.J.
CORPORATE SOURCE: G.J. Barritt, Department of Medical Biochemistry, School of Medicine, Flinders University, G.P.O. Box 2100, Adelaide, SA 5001, Australia. Greg.Barritt@flinders.edu.au
SOURCE: Biochemical Journal, (15 Jul 2003) 373/2 (327-336). Refs: 52
ISSN: 0264-6021 CODEN: BIJOAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The TRPC1 (transient receptor potential canonical 1) protein, which is thought to encode a non-selective cation channel activated by store depletion and/or an intracellular messenger, is expressed in a number of non-excitable cells. However, the physiological functions of TRPC1 are not well understood. The aim of these studies was to investigate the function of TRPC1 in liver cells using small interfering RNA (siRNA) to ablate the TRPC1 protein. Treatment of H4-IIE liver cells with siRNA targeted against TRPC1 caused an approx. 50% decrease in expression of the human TRPC1 protein in cells transfected with cDNA encoding human TRPC1, and a 50% decrease in expression of the endogenous TRPC1 protein (assessed by Western blot and immunofluorescence). The decrease in endogenous TRPC1 protein in cells transfected with TRPC1 siRNA was associated with a greater increase in cell volume (compared with the increase observed in control cells) immediately after cells were placed in a hypotonic medium, and an enhanced regulatory cell volume decrease after exposure to hypotonic medium. Treatment with siRNA targeted against TRPC1 also led to a 25% inhibition of thapsigargin-stimulated Ca(2+) inflow, a 40% inhibition of ATP and maitotoxin-stimulated Ca(2+) inflow, and a 50% inhibition of maitotoxin-stimulated Mn(2+) inflow. The idea that, in liver cells, TRPC1 encodes a non-selective cation channel involved directly or indirectly in the regulation of cell volume is consistent with the results obtained.

L9 ANSWER 41 OF 49 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003269022 EMBASE
TITLE: RNA interference reveals that endogenous Xenopus MinK-related peptides govern mammalian K(+) channel function in oocyte expression studies.
AUTHOR: Anantharam A.; Lewis A.; Panaghie G.; Gordon E.; McCrossan Z.A.; Lerner D.J.; Abbott G.W.
CORPORATE SOURCE: G.W. Abbott, Weill Med. Coll. of Cornell Univ., Starr 463,

520 E. 70th St., New York, NY 10021, United States.
gwa2001@med.cornell.edu
SOURCE: Journal of Biological Chemistry, (4 Apr 2003) 278/14 (11739-11745).
Refs: 44
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The physiological properties of most ion channels are defined experimentally by functional expression of their pore-forming α subunits in Xenopus laevis oocytes. Here, we cloned a family of Xenopus KCNE genes that encode MinK-related peptide K(+) channel β subunits (xMiRPs) and demonstrated their constitutive expression in oocytes. Electrophysiological analysis of xMiRP2 revealed that when overexpressed this gene modulates human cardiac K(+) channel α subunits HERG (human ether-ago-go-related gene) and KCNQ1 by suppressing HERG currents and removing the voltage dependence of KCNQ1 activation. The ability of endogenous levels of xMiRP2 to contribute to the biophysical attributes of overexpressed mammalian K(+) channels in oocyte studies was assessed next. Injection of an xMiRP2 sequence-specific short interfering RNA (siRNA) oligo reduced endogenous xMiRP2 expression 5-fold, whereas a control siRNA oligo had no effect, indicating the effectiveness of the RNA interference technique in Xenopus oocytes. The functional effects of endogenous xMiRP2 silencing were tested using electrophysiological analysis of heterologously expressed HERG channels. The RNA interference-mediated reduction of endogenous xMiRP2 expression increased macroscopic HERG current as much as 10-fold depending on HERG cRNA concentration. The functional effects of human MiRP1 (hMiRP1)/HERG interaction were also affected by endogenous xMiRP2. At high HERG channel density, at which the effects of endogenous xMiRP2 are minimal, hMiRP1 reduced HERG current. At low HERG current density, hMiRP1 paradoxically up-regulated HERG current, a result consistent with hMiRP1 rescuing HERG from suppression by endogenous xMiRP2. Thus, endogenous Xenopus MiRP subunits contribute to the baseline properties of K(+) channels like HERG in oocyte expression studies, which could explain expression level- and expression system-dependent variation in K(+) channel function.

L9 ANSWER 42 OF 49 EMBASE
on STN
ACCESSION NUMBER: 2003266283 EMBASE
TITLE: In vivo analysis of the RNA interference mechanism in Trypanosoma brucei.
AUTHOR: Tschudi C.; Djikeng A.; Shi H.; Ullu E.
CORPORATE SOURCE: E. Ullu, Department of Internal Medicine, Yale University Medical School, 333 Cedar Street, New Haven, CT 06520-8022, United States. elisabetta.ullu@yale.edu
SOURCE: Methods, (1 Aug 2003) 30/4 (304-312).
Refs: 20
ISSN: 1046-2023 CODEN: MTHDE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Flagellate protozoa of the family Trypanosomatidae, which includes various members of the genera Leishmania and Trypanosoma, are model systems for unicellular pathogens to study fundamentally important biological phenomena. Recently, ablation of gene expression by RNA interference (RNAi) has become the method of choice to study

gene function in Trypanosoma brucei, an early divergent eukaryote that infects humans and animals. As has been shown in multicellular organisms, the RNAi mechanism in T. brucei involves processing of double-stranded RNA 24- to 26-nt RNAs, termed small interfering RNAs (siRNAs), which guide degradation of the target mRNA. In this article, we describe some of the methods we employ for the analysis of the RNAi mechanism in T. brucei with particular emphasis on detection, cloning, and fractionation of siRNAs and siRNA complexes.

L9 ANSWER 43 OF 49 EMBASE on STN

ACCESSION NUMBER: 2003253881 EMBASE
TITLE: Activation of the tumour suppressor kinase LKB1 by the STE20-like pseudokinase STRAD.
AUTHOR: Baas A.F.; Boudeau J.; Sapkota G.P.; Smit L.; Medema R.; Morrice N.A.; Alessi D.R.; Clevers H.C.
CORPORATE SOURCE: H.C. Clevers, Hubrecht Laboratory, Centre for Biomedical Genetics, Uppsalalaan 8, 3584 CT Utrecht, Netherlands. clevers@niob.knaw.nl
SOURCE: EMBO Journal, (16 Jun 2003) 22/12 (3062-3072).
Refs: 41
ISSN: 0261-4189 CODEN: EMJODG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The LKB1 gene encodes a serine/threonine kinase mutated in Peutz-Jeghers cancer syndrome. Despite several proposed models for LKB1 function in development and in tumour suppression, the detailed molecular action of LKB1 remains undefined. Here, we report the identification and characterization of an LKB1-specific adaptor protein and substrate, STRAD (STe20 Related ADaptor). STRAD consists of a STE20-like kinase domain, but lacks several residues that are indispensable for intrinsic catalytic activity. Endogenous LKB1 and STRAD form a complex in which STRAD activates LKB1, resulting in phosphorylation of both partners. STRAD determines the subcellular localization of wild-type, but not mutant LKB1, translocating it from nucleus to cytoplasm. One LKB1 mutation previously identified in a Peutz-Jeghers family that does not compromise its kinase activity is shown here to interfere with LKB1 binding to STRAD, and hence with STRAD-dependent regulation. Removal of endogenous STRAD by siRNA abrogates the LKB1-induced G(1) arrest. Our results imply that STRAD plays a key role in regulating the tumour suppressor activities of LKB1.

L9 ANSWER 44 OF 49 EMBASE on STN

ACCESSION NUMBER: 2003208857 EMBASE
TITLE: TACE cleavage of proamphiregulin regulates GPCR-induced proliferation and motility of cancer cells.
AUTHOR: Gschwind A.; Hart S.; Fischer O.M.; Ullrich A.
CORPORATE SOURCE: A. Ullrich, Department of Molecular Biology, Max-Planck Institute of Biochemistry, Am Klopferspitz 18A, D-82152 Martinsried, Germany. ullrich@biochem.mpg.de
SOURCE: EMBO Journal, (15 May 2003) 22/10 (2411-2421).
Refs: 49
ISSN: 0261-4189 CODEN: EMJODG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Communication between G protein-coupled receptor (GPCR) and epidermal growth factor receptor (EGFR) signalling systems involves cell surface proteolysis of EGF-like precursors. The underlying mechanisms of EGFR signal transactivation pathways, however, are largely unknown. We demonstrate that in squamous cell carcinoma cells, stimulation with the GPCR agonists LPA or carbachol specifically results in metalloprotease cleavage and release of amphiregulin (AR). Moreover, AR gene silencing by siRNA or inhibition of AR biological activity by neutralizing antibodies and heparin prevents GPCR-induced EGFR tyrosine phosphorylation, downstream mitogenic signalling events, cell proliferation, migration and activation of the survival mediator Akt/PKB. Therefore, despite some functional redundancy among EGF family ligands, the present study reveals a distinct and essential role for AR in GPCR-triggered cellular responses. Furthermore, we present evidence that blockade of the metalloprotease-disintegrin tumour necrosis factor-α-converting enzyme (TACE) by the tissue inhibitor of metalloprotease-3, a dominant-negative TACE mutant or RNA interference suppresses GPCR-stimulated AR release, EGFR activation and downstream events. Thus, TACE can function as an effector of GPCR-mediated signalling and represents a key element of the cellular receptor cross-talk network.

L9 ANSWER 45 OF 49 EMBASE
on STN
ACCESSION NUMBER: 2003189597 EMBASE
TITLE: Protein Phosphorylation Drug Discovery Summit - SRI conference: Targeting kinases and phosphatases for novel therapeutics: 3-5 March 2003, San Diego, CA, USA.
AUTHOR: Hooft R.
CORPORATE SOURCE: R. Hooft, Serono Pharmaceut. Res. Institute, 14 Chemin des Aulx, 1228 Plan-les-Ouates, Geneva, Switzerland. rob.hooft@serono.com
SOURCE: IDrugs, (1 Apr 2003) 6/4 (312-314).
ISSN: 1369-7056 CODEN: IDRUFN
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
029 Clinical Biochemistry
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB These two new classes of targets (phosphatases and E3 ligases) have gained credibility in the relatively short time since their identification, while PTP1B continues to be the principal focus of the phosphatase community. The fact that PTP1B can be targeted with a once-daily injection of antisense suggests it is a highly 'sensitive' target. The unique advantage of the antisense compound is that it is likely to be highly selective among phosphatases. The competition for orally available formulations cannot match this selectivity today. Therefore, if selectivity is indeed crucial (and PTP1B is a good target in humans as well), then the antisense drug has better prospects. The antisense compound also appears to be quite potent, as once-weekly or even less frequent injections are effective in animal models. On the other hand, the success of Isis appears to indicate that PTP1B is a 'sensitive' target that may not require 100% inhibition. This, in turn, could mean that an orally available 'conventional' inhibitor need not have absolute selectivity. For other PTPs, target validation remains the bottleneck. The E3 ligases appear a powerful handle to regulate protein activity. The E3 family diversity, which easily exceeds the diversity of kinases, combined with systematic siRNA-based approaches to find the critical targets is another

promise in the war on cancer, but one that will undoubtedly also benefit other disease areas.

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ACCESSION NUMBER: 2003149526 EMBASE
TITLE: Modulation of p53 and p73 levels by cyclin G: Implication of a negative feedback regulation.
AUTHOR: Ohtsuka T.; Ryu H.; Minamishima Y.A.; Ryo A.; Lee S.W.
CORPORATE SOURCE: S.W. Lee, Harvard Institutes of Medicine, 77 Avenue Louis Pasteur, Boston, MA 02115, United States. slee2@caregroup.harvard.edu
SOURCE: Oncogene, (20 Mar 2003) 22/11 (1678-1687).
Refs: 37
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Cyclin G is a transcriptional target gene of tumor suppressor p53. Recent studies present evidence that cyclin G may play a central role in the p53-Mdm2 autoregulated module, but the precise function of cyclin G remains elusive. Here, we show a negative effect of cyclin G on the stability of p53 and p73. Cyclin G expression resulted in a dramatic decrease of p53 protein levels in response to DNA damage and abrogated irradiation-mediated G1 arrest along with an increase of S phase in MCF7 cells containing wild-type p53. In p53-null Saos2 cells, cyclin G inhibited p73 induction in response to genotoxic stress and delayed the camptothecin-mediated cell cycle arrest. Cyclin G interacts with p53 as well as p73, and its binding to p53 or p73 presumably mediates downregulation of p53 and p73. We also found that cyclin G-mediated reduction of p53 but not of p73 is Mdm2-dependent. Moreover, inhibition of cyclin G by small interfering RNA (siRNA) caused the accumulation of p53 and p73 protein levels in response to DNA damage. Therefore, our results imply that cyclin G is transcriptionally activated by p53 or p73, and, in turn, cyclin G negatively regulates the stabilization of p53 family proteins through an unknown mechanism different from ubiquitination or transcriptional control.

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ACCESSION NUMBER: 2002392549 EMBASE
TITLE: Silencing of Bruton's tyrosine kinase (Btk) using short interfering RNA duplexes (siRNA).
AUTHOR: Heinonen J.E.; Smith C.I.E.; Nore B.F.
CORPORATE SOURCE: C.I.E. Smith, Clinical Research Center (CRC), Karolinska Institutet, Huddinge University Hospital, SE-141 86 Huddinge, Sweden. edvard.smith@crc.ki.se
SOURCE: FEBS Letters, (11 Sep 2002) 527/1-3 (274-278).
Refs: 26
ISSN: 0014-5793 CODEN: FEBLAL
PUBLISHER IDENT.: S 0014-5793(02)03206-4
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Tec family tyrosine kinases, Bruton's tyrosine kinase (Btk),

Itk, Bmx, Tec, and Txk, are multi-domain proteins involved in hematopoietic signaling. Here, we demonstrate that human Btk protein can transiently be depleted using double-stranded short RNA interference (siRNA) oligonucleotides. Imaging and Western blotting analysis demonstrate that Btk expression is down regulated in heterologous systems as well as in hematopoietic lineages, following transfection or microinjection of Btk siRNA duplexes. The induction of histamine release, a pro-inflammatory mediator, in RBL-2H3 mast cells was reduced by 20-25% upon Btk down regulation. Similar, results were obtained when the Btk activity was inhibited using the kinase blocker LFM-A13. These results demonstrate a direct role of Btk for the efficient secretion of histamine in allergic responses.

L9 ANSWER 48 OF 49 EMBASE on STN

ACCESSION NUMBER: 2002308288 EMBASE
TITLE: A role of the C-terminal region of human Rad9 (hRad9) in nuclear transport of the hRad9 checkpoint complex.
AUTHOR: Hirai I.; Wang H.-G.
CORPORATE SOURCE: H.-G. Wang, Drug Discovery Program, H. L. Moffitt Cancer Ctr./Res. Inst., 12902 Magnolia Dr., Tampa, FL 33612, United States. wanghg@moffitt.usf.edu
SOURCE: Journal of Biological Chemistry, (12 Jul 2002) 277/28 (25722-25727).
Refs: 40
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Rad9, Rad1, and Hus1 are members of the Rad family of checkpoint proteins that are required for both DNA replication and DNA damage checkpoints and are thought to function as sensors in the DNA integrity checkpoint control. These proteins can interact with each other and form a stable proliferating cell nuclear antigen-related Rad9.ovrhdot.Rad1.ovrhdot.Hus1 heterotrimeric complex that might encircle DNA at or near the damaged sites. In this study, we demonstrate that the human Rad9 (hRad9) protein contains a predicted nuclear localization sequence (NLS) near its C terminus, which plays an essential role in the hRad9-mediated G2 checkpoint. Deletion experiments indicate that the NLS-containing region of hRad9 is critical for the nuclear transport of not only hRad9 but also human Rad1 (hRad1) and human Hus1 (hHus1), although this region is not required for hRad9.ovrhdot.hRad1.ovrhdot.hHus1 complex formation. In support of the role that hRad9 NLS plays in the nuclear targeting of the hRad9.ovrhdot.hRad1.ovrhdot.hHus1 complex, overexpression of a deletion mutant of hRad9 lacking the NLS-containing C-terminal region can bypass the G2 checkpoint and result in cell death after ionizing radiation or hydroxyurea treatment. Moreover, knockdown of hRad9 expression by small interfering RNA (siRNA) results in hRad1 accumulation in the cytoplasm and significantly abrogates the G2 checkpoint in the presence of damaged DNA or incomplete DNA replication. Thus, the C-terminal region of human Rad9 protein is important for G2 checkpoint control by operating the transport of the hRad9.ovrhdot.hRad1.ovrhdot.hHus1 checkpoint complex into the nucleus.

L9 ANSWER 49 OF 49 WPIDS on STN

ACCESSION NUMBER: 2003-804036 [75] WPIDS
DOC. NO. CPI: C2003-222009
TITLE: Prolonging expression of a heterologous gene in a cell

infected with a vector encoding the heterologous gene, useful for treating cancer, comprises infecting the cell with a vector encoding an apoptosis inhibiting agent.

DERWENT CLASS: B04 D16
INVENTOR(S): SCHWARTZ, P S; WAXMAN, D J
PATENT ASSIGNEE(S): (UYBO-N) UNIV BOSTON
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003083052	A2	20031009	(200375)*	EN	96

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2003224732	A1	20031013	(200435)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003083052	A2	WO 2003-US8743	20030325
AU 2003224732	A1	AU 2003-224732	20030325

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2003224732	A1	Based on	WO 2003083052

PRIORITY APPLN. INFO: US 2002-367311P 20020325
AN 2003-804036 [75] WPIDS
AB WO2003083052 A UPAB: 20031120
NOVELTY - Prolonging expression of a heterologous gene in a cell infected with a vector encoding the heterologous gene comprising infecting the cell with a vector encoding an apoptosis inhibiting agent, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) increasing the concentration of a chemotherapeutic drug in, or in the vicinity of, a target cell in a mammal;

(2) increasing the concentration of a soluble or secretable therapeutic factor in a target cell in a mammal; and

(3) increasing vector spread in a host containing a vector encoding a heterologous gene.

ACTIVITY - Cytostatic.
No biological data given.
MECHANISM OF ACTION - Apoptosis-Inhibitor; Gene therapy.
USE - The method is useful in increasing the concentration of a chemotherapeutic agent in a target cellular environment (e.g. cancer cells) or in inhibiting apoptotic cell death to enhance transgene expression, such as gene-directed enzyme/prodrug therapy.
Dwg.0/9

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FULL ESTIMATED COST	109.53	234.11

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LAST RELOADED: Mar 11, 2005 (20050311/UP).

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FULL ESTIMATED COST                                     2.64     236.75

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CA SUBSCRIBER PRICE                                     0.00     -10.22

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=> e wong-staal/au

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E2            1     WONG ZIYOUNG/AU
E3            0 --> WONG-STAAL/AU
E4            1     WONGA C S/AU
E5            1     WONGA CHEUK YIN/AU
E6            1     WONGA M V/AU
E7            1     WONGA W/AU
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E10          14     WONGARN R/AU
E11          14     WONGARN RENU/AU
E12           1     WONGARSA C/AU

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E9            2     WONGANUCHITMETA SAENG NGAM/AU
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E12           1      WONGARSA C/AU

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E8            1      STAAL A S NORSK/AU
E9           20      STAAL ADA/AU
E10           2      STAAL AKTIESELSKAPET NORSK/AU
E11           5      STAAL ANNE/AU
E12           9      STAAL B/AU

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L10           0 STAAL WONG/AU

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E5            7      STAAL WOUTER G/AU
E6            9      STAAL Y C M/AU
E7            1      STAALAND D H/AU
E8           72      STAALAND H/AU
E9           21      STAALAND HANS/AU
E10           3      STAALAND T/AU
E11           1      STAALAND THERESIA/AU
E12           4      STAALBERG E/AU

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L11           0 WONG STAAL/AU

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E2            1      WONG SOW LONG/AU
E3            0 --> WONG STAAL/AU
E4         1077      WONG STAAL F/AU
E5            3      WONG STAAL F F/AU
E6            3      WONG STAAL F Y/AU
E7            1      WONG STAAL FLORRIE/AU
E8          448      WONG STAAL FLOSSIE/AU
E9            1      WONG STAAL FLOSSIE F/AU
E10           1      WONG STAAL FLOSSIE Y/AU
E11           2      WONG STAAL FLOSSIE YEECHING/AU
E12           1      WONG STAAL Y/AU

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                 OR "WONG STAAL FLORRIE"/AU OR "WONG STAAL FLOSSIE"/AU OR "WONG
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                FLOSSIE YEECHING"/AU)

=> siRNA and l12
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L13          12 SIRNA AND L12

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14           6 DUP REM L13 (6 DUPLICATES REMOVED)

=> t ti l14 1-6

L14  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Protein and cDNA sequences of nuclear receptors NR4A1, NR4A12, NR4A3,
     NR2F6 and NR2F1 and methods of inhibiting cancer growth using siRNAs

L14  ANSWER 2 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN  DUPLICATE 1
TI   Construction of small interfering RNA expression cassette libraries for
     selective post-transcriptional silencing of gene families and their
     therapeutic application

L14  ANSWER 3 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN  DUPLICATE 2
TI   Construction of small interfering RNA expression cassettes and expression
     libraries under control of a single RNA polymerase III promoter using a
     polymerase primer hairpin linker

L14  ANSWER 4 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN  DUPLICATE 3
TI   dual pol III promoter cassette for transcription of small interfering RNA
     (siRNA) library and uses

L14  ANSWER 5 OF 6     MEDLINE on STN                  DUPLICATE 4
TI   Relative gene-silencing efficiencies of small interfering RNAs targeting
     sense and antisense transcripts from the same genetic locus.

L14  ANSWER 6 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN
TI   Ribozymes in gene identification, target validation and drug discovery


=> d ibib abs l14 1-6

L14  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:158776  CAPLUS
TITLE:                    Protein and cDNA sequences of nuclear receptors NR4A1,
                          NR4A12, NR4A3, NR2F6 and NR2F1 and methods of
                          inhibiting cancer growth using siRNAs
INVENTOR(S):              Li, Henry; Ke, Ning; Grifman, Mirta; Claassen, Gisela;
                          Hu, Xiuyuan; Defife, Kristin; Habita, Cellia; Fan,
                          Wufang; Rhoades, Kristina; Tan, Philip;
                          Wong-Staal, Flossie
PATENT ASSIGNEE(S):       Immusol Incorporated, USA
SOURCE:                   PCT Int. Appl., 94 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
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     WO 2005017112         A2    20050224    WO 2004-US23821          20040723
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             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
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AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-492618P P 20030805

AB The present invention provides methods for identifying agents useful for inhibiting cancer cells by binding to various nuclear receptor proteins, or to the genes or RNA encoding such proteins. These nuclear receptor proteins include NR4A1-3, NR2F6 and NR2F1. In particular embodiments, the knockdown of all these nuclear receptor proteins expressed in cancerous tissue, as well as the genes or mRNA encoding such proteins, is demonstrated to inhibit growth and/or proliferation of cancer cells.

L14 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:698226 CAPLUS

DOCUMENT NUMBER: 141:219942

TITLE: Construction of small interfering RNA expression cassette libraries for selective post-transcriptional silencing of gene families and their therapeutic application

INVENTOR(S): Li, Henry; Chatterton, Jon E.; Fan, Wufang; Ke, Ning; Wong-Staal, Flossie

PATENT ASSIGNEE(S): Immusol Incorporated, USA

SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004072261	A2	20040826	WO 2004-US3949	20040210
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI				
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US 2005026172	A1	20050203	US 2004-776399	20040210

PRIORITY APPLN. INFO.: US 2003-446714P P 20030211

AB The present invention provides methods for construction of small interfering RNA expression cassette libraries for selective post-transcriptional silencing of gene families and their therapeutic application. The invention includes family of proteins known to be involved in disease such as G protein coupled receptors, ion channels, receptor tyrosine kinases, non-receptor tyrosine kinases, nuclear hormone receptors, GTPases, ATPases, serine/threonine kinase, proteases, matrix metalloproteinase, GTPase activating protein, E3 ubiquitin ligase.

L14 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2004:80858 CAPLUS

DOCUMENT NUMBER: 140:140656

TITLE: Construction of small interfering RNA expression cassettes and expression libraries under control of a single RNA polymerase III promoter using a polymerase primer hairpin linker

INVENTOR(S): Li, Henry; Chatterton, Jon E.; Ke, Ning; Rhoades, Kristina L.; Wong-Staal, Flossie
PATENT ASSIGNEE(S): Immusol Incorporated, USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009796	A2	20040129	WO 2003-US23239	20030723
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004115815	A1	20040617	US 2003-628587	20030723
PRIORITY APPLN. INFO.:			US 2002-399040P	P 20020724

AB The invention claims methods for construction of small interfering RNA (siRNA) expression cassettes using a polymerase primer hairpin linker. The expression cassette is constructed from a self-priming oligonucleotide comprising three segments (from 5' to 3' direction): (1) a 5' leader sequence between 4 and 27 nucleotides long with at least four consecutive adenylyl residues (complementary to the polIII transcription terminator) at its 3' end, (2) a coding sequence for the sense strand of an siRNA, preferably 11-27 nucleotides, and (3) a polymerase primer hairpin linker. The 5' leader sequence can include restriction site(s) for cloning siRNA coding sequences into expression cassettes. The polymerase primer hairpin linker forms a short stem-loop structure involving the 3' end of the self-priming oligonucleotide. The sequence encoding the corresponding antisense strand of the siRNA and the complement of the 5' leader sequence are produced by primer extension from the 3' end of the polymerase primer hairpin linker. The product of the primer extension reaction includes a stem-loop that must be denatured. Blocking primers are then annealed to the 5' and 3' ends of the denatured DNA. A complementary strand for the entire mol. is synthesized, thereby producing a duplex DNA that can be used to complete the construction of the expression cassette. The methods allow rapid construction of a single transcriptional unit encoding both strands of a hairpin siRNA, regardless of sequence. Expression cassettes of the invention contain an RNA polymerase III-dependent promoter and regulatory elements for inducible transcription of siRNAs. In addition, the invention includes libraries comprising the expression cassettes of the invention, including vectors for transforming cells, such as replication-deficient retroviral vectors. Methods of the invention and siRNA expression vectors may be useful for elucidation of gene function and identification of novel genes. Specifically, the present invention relates to methods and compns. for improved functional genomic screening, functional inactivation of specific essential or non-essential genes, and identification of genes that are modulated in response to specific stimuli or encode recognizable phenotypic traits. The examples of the invention describe construction of a randomized siRNA gene library under control of a U6 snRNA promoter, construction of an siRNA expression vector with a tetracycline-inducible promoter, and down-regulation of firefly luciferase in a breast cancer cell line (MCF7-luc) by plasmid pLPR-U6-lucB-siRNAh. Another example describes use

of a hairpin siRNA gene library to enrich for siRNAs that down-regulate surface CD4 expression in the human T cell line, Molts-4.

L14 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:80856 CAPLUS
DOCUMENT NUMBER: 140:140740
TITLE: dual pol III promoter cassette for transcription of small interfering RNA (siRNA) library and uses
INVENTOR(S): Li, Henry; Chatterton, Jon E.; Ke, Ning; Wong-Staal, Flossie
PATENT ASSIGNEE(S): Immusol, Inc., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009794	A2	20040129	WO 2003-US23157	20030723
WO 2004009794	A3	20040624		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004146858	A1	20040729	US 2003-626512	20030723
PRIORITY APPLN. INFO.:			US 2002-398915P	P 20020724

AB The present invention provides expression cassettes comprising a novel dual promoter transcription system to generate small interfering RNA (siRNA). This system can be used to study gene function and the identification of novel genes. The a random double-stranded DNA sequences are cloned in between the pol III promoters. Each pol III promoter has a TATA box, and modified by substitution. One substitution places at least four adenylyl residues 3' to the TATA box. Such transcription cassettes result in production of a dsRNA with a 3' overhang of two or more nucleotides when the dsDNA sequence is transcribed from both polIII promoters. Other promoters, such as H1 RNA promoters, U6 snRNA promoters, are also included. The two promoters of the invention may be same promoters or they may be different. This system could be used for studying gene functions such as cell devision, viral gene expression, protein excretion, signal transduction, or apoptosis.

L14 ANSWER 5 OF 6 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004428831 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15333693
TITLE: Relative gene-silencing efficiencies of small interfering RNAs targeting sense and antisense transcripts from the same genetic locus.
AUTHOR: Hu Xiuyuan; Hipolito Sharlene; Lynn Rebecca; Abraham Violet; Ramos Silvester; Wong-Staal Flossie
CORPORATE SOURCE: Immusol Incorporation, 10790 Roselle Street, San Diego, CA 92121, USA.. hu@immusol.com
SOURCE: Nucleic acids research, (2004) 32 (15) 4609-17. Electronic Publication: 2004-08-27.
Journal code: 0411011. ISSN: 1362-4962.

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200409
ENTRY DATE: Entered STN: 20040831
Last Updated on STN: 20040911
Entered Medline: 20040910

AB Short interfering RNAs (siRNAs) directed against different regions of genes display marked variation in their potency in mediating mRNA degradation. Various factors have been proposed to affect the efficacy of siRNA. We explored some of the factors by evaluating in cultured human cells 28 randomly selected siRNAs targeting the GPR39 and MGC29643 transcripts derived from the same genetic locus but transcribed in opposite directions. Twenty of the 24 siRNAs targeting the overlapping regions of the transcripts simultaneously reduced the levels of both transcripts. Single nucleotide changes in either of the siRNA strands significantly reduced the gene-silencing efficiency of the siRNA on targeted sense transcript without affecting the antisense transcript. Overall, we observed a greater gene-silencing efficiency on the MGC29643 transcript than on the GPR39 transcript in HeLa cells. Since MGC29643 transcript is more abundant than the GPR39 transcript [0.24 versus 0.008% relative to 100% for glyceraldehyde-3-phosphate dehydrogenase (GAPDH)], the results suggest that the abundance of the mRNA affects the efficiency of silencing. Two additional observations supported this hypothesis. First, GAPDH whose intracellular level is the highest of the three was the most efficiently silenced. Second, a reversal of gene-silencing efficiency was observed in U-138 MG cells in which the relative abundance of the GPR39 and MGC29643 transcripts is also reversed. Our study suggests that low-abundant transcripts are less susceptible to siRNA-mediated degradation than medium- and high-abundant transcripts.

L14 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:175576 CAPLUS
DOCUMENT NUMBER: 140:351173
TITLE: Ribozymes in gene identification, target validation and drug discovery
AUTHOR(S): Chatterton, Jon E.; Hu, Xiuyuan; Wong-Staal, Flossie
CORPORATE SOURCE: Immusol, San Diego, CA, 92121, USA
SOURCE: Drug Discovery Today: Targets (2004), 3(1), 10-17
CODEN: DDTTA4; ISSN: 1741-8372
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Modern genomics technologies have facilitated the rapid correlation of gene expression data and disease phenotype to identify potential drug targets. Validation of these targets requires direct evidence for a causal, as opposed to merely correlative, relationship between expression level and phenotype. Sequence-specific gene silencing (using antisense, ribozymes and siRNA) has emerged as a powerful tool in the validation process. Although siRNA threatens to eclipse other gene-silencing methods, recent advances in ribozyme technol. should allow this approach to maintain a place in the target validation toolbox. Furthermore, combinatorial ribozyme libraries have proven invaluable for identifying functionally relevant genes.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L2           142 PY>2003 AND L1
L3            36 L1 NOT L2
L4            25 DUP REM L3 (11 DUPLICATES REMOVED)

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     MAR 2005
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L7           100 L5 NOT L6
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L9            49 L8 NOT L4

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L12          1531 E4-E11
L13            12 SIRNA AND L12
L14             6 DUP REM L13 (6 DUPLICATES REMOVED)

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